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ANNALS OF
INTERNAL MEDICINE

VOLUME 13 FEBRUARY, 1940 NUMBER 8

CHEMICAL CHANGES IN THE BLOOD OF PATIENTS WITH PYLORIC OBSTRUCTION *

By PAUL H. NOTH, M.D.,† and DWIGHT L. WILBUR, M.D., F.A.C.P.,‡
Rochester, Minnesota

FOR a long time clinicians and surgeons have appreciated the fact that a close relationship exists between loss of gastric and duodenal content by vomiting or through a fistula and changes in the chemical composition of the plasma of the blood. The importance of recognizing these changes in patients suffering from pyloric obstruction in whom surgical treatment is to be carried out has been amply proved by the reduction in mortality which has followed adequate preoperative preparation of patients. While the mechanisms leading to some of the chemical changes, for example, elevation of the values for urea content of the blood, have not been clearly established, fortunately therapeutic measures such as administration of a physiologic solution of sodium chloride have proved adequate in most cases to return the urea and the serum electrolytes to normal or relatively normal levels.

In the usual cases of pyloric obstruction the characteristic changes in the composition of the blood include a decrease in the level of chlorides in the plasma, an increase in the values for urea nitrogen in the blood and an increase in the power of the blood to combine with carbon dioxide. The decrease in the plasma chlorides has been explained as a result of loss of chlorides by vomiting or through the intestine, of shift of chlorides from the blood to the tissues or of possible shift of chlorides from the plasma to the corpuscles. The mechanisms leading to an elevation of the content of nonprotein nitrogen in the blood are less clearly understood than are those resulting in decreased values for plasma chlorides. However, the following factors have been considered at various times to be of etiologic significance: (1) increased destruction of body protein due to the effect of some toxic substance or as a result of dehydration; (2) decreased function of the kid-

* Submitted for publication August 24, 1938.
† Now residing in Detroit, Michigan.
‡ Now residing in San Francisco, California.

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neys resulting from dehydration or "toxic nephritis"; (3) hypochloremia resulting in elevation of the level of urea as a compensatory mechanism for maintaining the osmotic pressure of the blood; (4) alkalosis following marked vomiting or the administration of alkalies for therapeutic purposes. The increase in the bicarbonate content of the blood seems to be a compensatory process due to loss of chloride ions. Peters and Van Slyke [1] have pointed out that "although chloride deficiency is the most prominent feature of pyloric obstruction, dehydration and base deficiency seem to have more critical significance and are the factors which are responsible for the most of the serious symptoms and death."

The present study has been made for the purpose of evaluating if possible the significance of certain clinical factors which may be of importance in producing changes in the blood in cases of pyloric obstruction.

Material Studied

The present study is based on the records of 151 patients suffering from duodenal or gastric ulcer or from gastric carcinoma complicated by pyloric obstruction, demonstrated by clinical or roentgenologic examination or by intubation of the stomach. The history of vomiting of large quantities of gastric content, usually containing retained food remnants, retention of abnormal quantities of barium during roentgenologic examination of the stomach, or the retention of over 300 c.c. of gastric content one hour after the Ewald test meal (normal 200 c.c. or less) has been considered as evidence of pyloric obstruction and gastric retention.

A certain number of patients with abnormal values in the blood have been purposely selected for study in the hope of determining the importance of clinical factors such as vomiting, the concentration of hydrochloric acid in the gastric juice and the extent of pyloric obstruction in leading to the development of chemical alterations in the blood. Consequently the material does not permit of an analysis for the frequency of occurrence of abnormal values for urea, chlorides, and carbon dioxide content in an unselected group of patients.

Table 1 indicates the sex and age incidence of the patients and the type of lesion which was present. Approximately two-thirds of the patients had pyloric obstruction as a result of a duodenal or gastric ulcer while in the remaining third carcinoma of the stomach produced the obstruction.

For all of the patients studies have been made of the values of at least one of the following: plasma chlorides expressed as sodium chloride, blood urea and carbon dioxide combining power of the blood. For many patients data have been obtained in regard to the levels of gastric acidity, the amount of retained content in the stomach, the amount of gastric content usually vomited and the duration of vomiting, as well as such factors as the percentage of hemoglobin, results of urinalysis, and roentgenologic and surgical observations. Consideration has been given also to certain additional

factors which might influence the chemical constituents of the blood, namely, renal changes due to arteriosclerotic renal or obstructing urinary lesions, and gastrointestinal hemorrhages.

Sufficient data could not be obtained to permit quantitative studies of the chloride and nitrogen metabolism of patients suffering from pyloric obstruction. It was hoped that the material studied would be sufficient to permit the evaluation in a gross way of certain of the factors which may influence chemical changes in the blood of these patients. It seemed reasonable to believe that the presence or absence of vomiting, and perhaps to some extent the amount of gastric content vomited, the duration of vomiting, the presence or absence of free hydrochloric acid and its concentration in the gastric content and the amount of retained content in the stomach might influence significantly the level of chemical substances in the blood. A correlation of such clinical data with the levels of the plasma chlorides, the blood urea and the carbon dioxide combining power of the blood has therefore been attempted.

TABLE I

Age and Sex of Patients and Type of Associated Lesion in 151 Cases of Pyloric Obstruction

Diagnosis	Sex	Age in years			Number of cases
		Average	Youngest	Oldest	
Carcinoma of stomach	Male	58.3	36	79	43
	Female	59.0	46	75	10
	Both sexes	58.4	36	79	53
Duodenal and gastric ulcer	Male	51.2	20	81	77
	Female	49.6	23	76	21
	Both sexes	50.9	20	81	98
Total	Both sexes	53.5	20	81	151

The patients have been divided into two groups, the first consisting of those who did not receive any treatment prior to estimation of the levels for plasma chlorides, blood urea and carbon dioxide combining power of the blood, the second consisting of patients each of whom received one or two intravenous injections of 1 liter of physiologic solution of sodium chloride and of 10 per cent *d*-glucose before the estimations of the chemical values in the blood were made.

RESULTS

Plasma Chlorides. For 133 of the patients the values for plasma chlorides estimated as sodium chloride were obtained. An attempt has been made to correlate the values for plasma chlorides in these patients with a

variety of clinical factors which it was felt might influence the level of plasma chlorides.

Factors which do not correlate: The values for hemoglobin, the specific gravity of the urine, the period over which the symptom of vomiting occurred, the volume of gastric content ordinarily vomited, the amount of retained gastric content and the concentration of free hydrochloric acid in the gastric content are factors which could not be correlated with the level of plasma chlorides. Negative results also followed attempts to correlate the plasma chloride levels with combinations of these factors such as: (1) the volume of gastric content ordinarily vomited and the free hydrochloric acid in the gastric content, (2) the duration of vomiting, the volume of gastric content usually vomited and the free hydrochloric acid in the gastric content, and (3) the degree of free hydrochloric acid in the gastric content and the amount of retained gastric content.

Factors which correlate: There is a correlation between the level of plasma chlorides and a factor which we have called the amount of vomiting, which is obtained by estimating the volume of gastric content ordinarily vomited, the frequency of vomiting and the period over which the symptom of vomiting occurred (table 2). The amount of vomiting has been graded

TABLE II

Relative Values for Plasma Chloride and Amount of Vomiting in Cases of Pyloric Obstruction

Amount of vomiting,* grade	Number of cases	Plasma chlorides				
		Lower than normal values		Values in the blood (mg. per 100 c.c.)		
		Number of cases	Per cent of cases	Mean	Lowest	Highest
0	19	4	21.1	597	520	635
1	32	9	28.1	593	510	648
2	38	17	44.7	580	460	650
3	44	26	59.1	549	370	660

* The amount of vomiting is a factor composed by estimating the volume of gastric content ordinarily vomited, the frequency of vomiting and the period over which the symptom of vomiting occurred. (See text.)

as follows: grade 0 indicates that vomiting did not occur; grade 1 indicates vomiting of small amounts of fluid two or three times a week, usually over a short period of time; grade 2 includes vomiting of small amounts of fluid almost daily or larger amounts of fluid occasionally, usually over a short period of time; grade 3 indicates that vomiting of large quantities of gastric

content occurred several times daily over a period of a week to months. Table 2 indicates that the greater the amount of vomiting, the larger is the percentage of cases with abnormally low chloride values and the lower the mean value for plasma chlorides determined as sodium chloride.

There are exceptions to these findings. Even in a group of selected patients such as that which is reported in this paper, in 41 per cent of those in whom vomiting grade 3 was present the values for plasma chlorides were within the normal range. The occurrence of abnormal values for plasma chlorides in cases without much vomiting is considerably less frequent as evidenced by the fact that in the 19 cases in which vomiting did not occur the values for plasma chlorides were essentially normal (mean 597 mg. per 100 c.c.; lowest 520 mg. per 100 c.c.; normal 570 to 620 mg. per 100 c.c.). These values are for both the treated and untreated cases.

The influence of treatment consisting of one or two intravenous injections of 1000 c.c. of physiologic solution of sodium chloride and of 10 per cent *d*-glucose is illustrated in figure 1. This figure shows clearly how rapidly the abnormal values may approach the normal after the parenteral administration of chlorides and fluid.

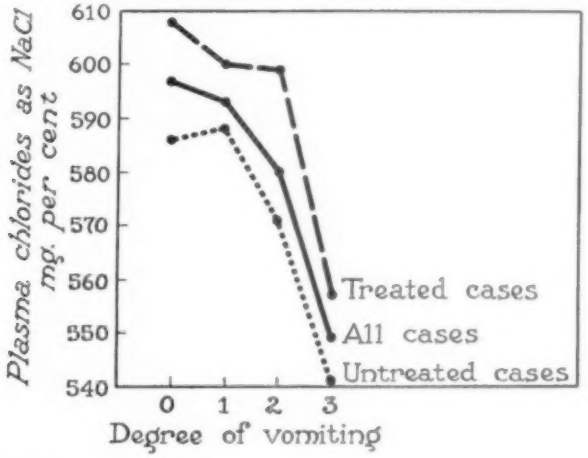

FIG. 1. Relation of plasma chlorides in blood of patients suffering from pyloric obstruction to degree of vomiting.

There is a definite correlation between the level of plasma chlorides and the carbon dioxide combining power of the blood (figure 2). The correlation of values for plasma chlorides and blood urea is discussed later in this paper.

Blood Urea. Factors which do not correlate: Attempts to correlate the values for the blood urea with such factors as the age of the patient, the amount of retained gastric content, the free hydrochloric acid content of the gastric juice and the carbon dioxide combining power of the blood proved

negative. Negative results also followed attempts to correlate the levels of blood urea with factors composed of multiples of any two of the following factors, namely, the amount of free hydrochloric acid in the gastric content, the amount of retained content in the stomach, the amount of vomiting and the degree of free hydrochloric acid in the gastric content.

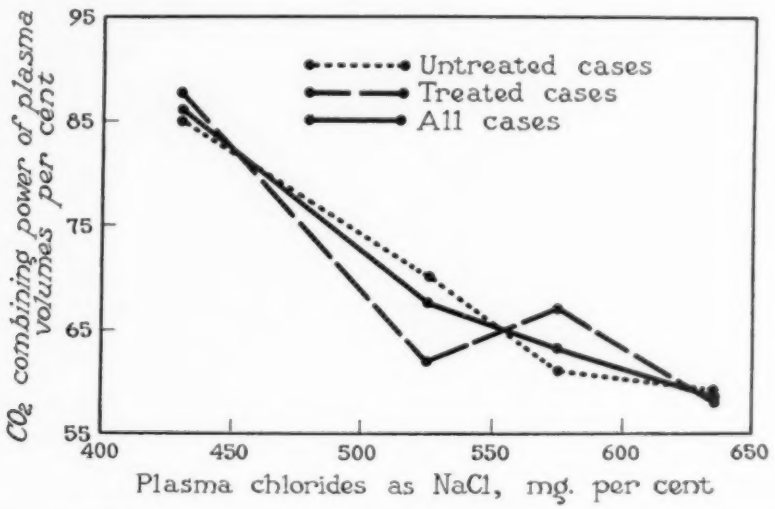

FIG. 2. Relation of the carbon dioxide combining power of the blood of patients suffering from pyloric obstruction to plasma chlorides.

Factors which correlate: We were able to establish a relation between the values for blood urea and the amount of vomiting (table 3) as was true

TABLE III

Relation of Values for Blood Urea and Amount of Vomiting in Cases of Pyloric Obstruction

Amount of vomiting, grade	Number of cases	Blood urea				
		Higher than normal values		Values in the blood (mg. per 100 c.c.)		
		Number of cases	Per cent of cases	Mean	Lowest	Highest
0	20	3	15.0	31	18	56
1	34	11	32.4	36	14	82
2	41	13	31.7	41	16	130
3	49	28	57.1	54	16	156
Total	144					

also for the plasma chlorides (table 2). The mean values for blood urea rose steadily with increases in the amount of vomiting. The values for blood urea were abnormally high in only three patients (15 per cent) of the 20 who did not vomit. That not all patients with marked vomiting have abnormal values for blood urea is indicated by the finding of normal values for urea in 43 per cent of patients with vomiting grade 3.

In general there was some correlation of the values for plasma chlorides and for blood urea as indicated by the observation that the lower the range of values for plasma chlorides the higher was the level for blood urea (table 4). In all of the 10 patients in whom the values for plasma chlorides were less than 500 mg. per 100 c.c., the values for blood urea were 40 mg. per 100 c.c. or more.

TABLE IV

Relation of the Values for Plasma Chloride to Those for Blood Urea in Cases of Pyloric Obstruction: Treated and Untreated Cases

Plasma chloride, values in mg. per 100 c.c.	Number of cases	Blood urea values in mg. per 100 c.c.		
		Mean	Highest	Lowest
500 or less	10	104.6	156	40
500–550	36	42.3	93	14
550–600	48	42.7	130	18
600 or more	57	32.9	80	14
Total	151			

Carbon Dioxide Combining Power of the Blood. Attempts to correlate the values for carbon dioxide combining power of the blood with many of the factors previously noted in the paragraphs on the plasma chlorides and blood urea gave essentially similar results. There was, however, definite correlation of the values for carbon dioxide combining power of the blood and the plasma chlorides as illustrated in figure 2.

Achlorhydria. Achlorhydria was present in 21 of the 151 patients. For most of these patients the values for gastric acidity were obtained one hour after an Ewald meal. In a few instances histamine was used as a gastric stimulant. Study of the values for plasma chlorides, blood urea and carbon dioxide combining power of the blood in patients with achlorhydria gave results essentially similar to those reported for the entire group of 151 patients.

In three of the 21 patients with achlorhydria the values for plasma chlorides were less than 580 mg. per 100 c.c. In one of these three patients vomiting did not occur, in another there was vomiting grade 2 and in the third vomiting grade 3. Four of the 17 patients with achlorhydria in whom

estimations of the values for blood urea were made had a level of urea over 50 mg. per 100 c.c. Vomiting was a prominent feature in all of these four cases (in three it was graded 3 and in one case graded 2).

Patients with Large Amounts of Retained Gastric Content. Analysis of the records of patients who retained a large amount of gastric content failed to reveal a greater proportion of these with abnormal chemical findings in the blood than of patients with slight retention; neither were such abnormal chemical changes more marked in patients who retained a large amount of gastric content than in patients who retained a smaller amount.

Gastrointestinal Hemorrhage. There were 20 patients in whom gross bleeding from the gastrointestinal tract had been of recent occurrence and in whom it was considered to be a complication in addition to pyloric obstruction. In this group of patients the mean value for blood urea was 54.5 mg. per 100 c.c. and for plasma chlorides 551.8 mg. per 100 c.c. (19 of 20 patients). This is in contrast with values for the entire group, which were as follows: for blood urea (144 patients) 40.5 mg. per 100 c.c., for plasma chlorides (133 patients) 579.75 mg. per 100 c.c.

Patients with Hypertrophy of the Prostate Gland and Urinary Obstruction. In 16 patients there was prostatic hypertrophy of sufficient degree to produce difficulty in urination. The mean value for blood urea in this group was 56.4 mg. per 100 c.c., for plasma chlorides 543 mg. per 100 c.c. (14 cases).

Influence of the Type of Lesion. There was no significant difference in the findings for the chemical changes in the blood in those patients in whom the pyloric obstruction was due to carcinoma of the stomach as compared with those in whom it was due to gastric or duodenal ulcer.

Influence of the Intravenous Administration of Solutions of Sodium Chloride and d-Glucose. The effect of treatment is apparent, for in those patients to whom such treatment was given the mean values for the blood urea were lower and for chlorides higher than in the group which did not receive treatment (figure 1).

Interpretation of Results

Plasma Chlorides. The decrease in values for plasma chlorides, which is one of the characteristic findings in the blood in many cases of pyloric obstruction, has been considered the result of loss of chlorides by vomiting or through the intestine (in patients suffering from diarrhea), of shift of chlorides from blood to tissue and of possible shift of chlorides from plasma to corpuscles in the blood.

The results obtained tend to substantiate the view that loss of chlorides by vomiting is an important and perhaps the most important factor leading to decreased values for chlorides in the plasma in cases of pyloric obstruction. In our results there was a definite relation between the amount of vomiting

and the decrease in values of plasma chlorides, for the greater the amount of vomiting the more likely was the value for plasma chlorides to be low. That loss of chlorides by vomiting is not the only factor which may influence the values for plasma chlorides in cases of pyloric obstruction is indicated by the fact that in some patients who did not vomit and in whom therefore presumably little if any loss of chlorides resulted from this source, the values for plasma chlorides were below normal, while in other patients with much vomiting and presumably loss of considerable amounts of chlorides, the values for chlorides in the plasma were essentially normal. It is possible, however, that a state of chloride deficiency may exist in some of these patients despite the normal values for plasma chlorides. A clear-cut relation could not be established between the amount of free hydrochloric acid in the gastric content and the level of plasma chlorides. One might anticipate that in patients with a high concentration of hydrochloric acid in the gastric juice and a large amount of vomiting and therefore presumably a greater loss of chlorides one would find greater changes in the values of plasma chlorides than in patients with a low concentration of hydrochloric acid in the gastric content. This, however, did not prove true. In fact in patients with achlorhydria, in whom one might anticipate loss of less chloride than in patients with free hydrochloric acid, the values for plasma chlorides were commensurate with those of the whole group. Studies of the neutral chlorides and total chlorides in the gastric juice were not made.

Other factors which may compensate for loss of chloride in these patients and explain the variable results include shift of chlorides from tissues to the blood or from corpuscles to plasma, changes in renal function leading to decreased output of chlorides in the urine, concentration of the plasma, and, lastly, variations in the intake of chlorides in the food and drink. Similarly, failure of or alterations in these compensatory mechanisms may lead to unexpected variations in the level of plasma chlorides. We have no data to indicate the importance of these various factors in this group of patients. Such information will have to come from quantitative data of the metabolism and balance of chlorides in patients suffering from pyloric obstruction.

The rather close correlation which exists between the levels of plasma chlorides and carbon dioxide combining power of the blood (figure 2) is easily understood, for as chloride ions are lost from or decrease in the plasma they are replaced in large part by bicarbonate ions. If the loss of chloride is continued or is marked, alkalosis may develop and eventually result in "gastric" tetany.

Blood Urea. The changes in the values for blood urea which are frequently found in patients suffering from pyloric obstruction have been explained as a result of the action of a toxic substance, of increased destruction of body proteins due to dehydration, of decreased function of the kidneys due to dehydration or "toxic nephritis," or of hypochloremia or alkalosis.

The results obtained in this study do not indicate which of these mechanisms is the most important. There is a definite relation between the amount

of vomiting and the values for blood urea. The greater the amount of vomiting, the more likely are the levels for blood urea to be elevated. This may be the result of the greater dehydration in these patients but the evidence is not conclusive. To some extent there is a correlation between the rise of blood urea and the drop of plasma chlorides but in a general way only, and the rise of urea cannot be considered a compensatory process to maintain osmotic relationships. Attempts to correlate elevation of values for blood urea with a variety of other factors previously mentioned proved unsuccessful.

Studies of the metabolism of nitrogen and urea in patients suffering from pyloric obstruction will be necessary before it will be possible to elucidate the rôle of the various mechanisms which may result in elevated values for blood urea.

Studies of the rôle which disturbed function of the kidneys may play in cases of pyloric obstruction were not complete. Examination of the urine in some of these cases reveals a high specific gravity, suggesting that the kidney function is unimpaired and that if changes of the blood occur they are the result of dehydration or other "pre-renal" factors which interfere with renal function. Previously reported [2] pathologic studies of the kidneys in cases of this type reveal as the outstanding abnormality degenerative changes of the tubules. The glomeruli generally appear essentially normal, and in this respect the kidneys are quite distinct from those obtained from cases of chronic glomerular nephritis, in which glomerular changes are outstanding. In the latter the retention of urea in the blood is thought to be due to the renal lesion.

It has generally been recognized that following a gastrointestinal hemorrhage there may be elevation of the values for urea in the blood. This rise has been thought to be due principally to dehydration. In our patients in whom gastrointestinal hemorrhages occurred in addition to pyloric obstruction, the mean values for blood urea were higher than in the group of patients without bleeding but no evidence has been obtained to explain this finding.

The effects of treatment on the chemical changes of the blood in pyloric obstruction are of particular interest. To some of the patients one or two intravenous injections of 1000 c.c. of physiologic solution of sodium chloride and 10 per cent of *d*-glucose were administered before estimations were made of the chemical constituents of the blood. In patients with slight changes of the blood one or two such injections were usually sufficient to restore the blood urea or plasma chlorides to normal levels, while, as might be anticipated, in patients in whom vomiting was large in amount and the changes in the blood marked, one or two intravenous injections had very little effect on the values of plasma chloride, blood urea and carbon dioxide combining power.

Clinical Value of the Results

From the practical standpoint the results of this study are of considerable interest. It is well recognized that patients suffering from pyloric obstruction frequently present abnormalities of the chemical composition of the blood and that these abnormalities can be readily overcome by treatment, which must be instituted preoperatively if operation is to be carried out with the minimal risk to the patient. Under what circumstances do these abnormalities of the chemical composition of the blood occur and what is to lead the physician to suspect their presence? The results of this study suggest that patients who vomit large amounts of gastric content frequently and over a considerable period of time are the ones most likely to show elevated values for blood urea and carbon dioxide combining power of the blood and decreased values for plasma chlorides. However, these changes may be found in the absence of vomiting, although this is unlikely.

According to the results of this study the type of lesion producing the obstruction, namely carcinoma of the stomach or gastric or duodenal ulcer, is not a significant factor nor is the presence or absence of free hydrochloric acid in the gastric content significant. The patients we have studied in whom achlorhydria was found presented changes essentially the same as did those patients in whom acid was present in the gastric juice. Similarly there was no significant difference in the values in the blood as between those patients who had a low concentration of free hydrochloric acid in the gastric juice and those patients in whom a high concentration of free hydrochloric acid was found.

It is probable that the alterations in the blood will be greater than those usually observed if in addition to pyloric obstruction there is gastrointestinal bleeding or hypertrophy of the prostate with urinary obstruction.

Physicians frequently wonder what studies of the blood chemistry should be made in cases of pyloric obstruction. Our results indicate that changes in the plasma chlorides and blood urea do not parallel one another except when the changes are marked—that is, if the value for plasma chloride is lower than 500 mg. per 100 c.c., the blood urea probably will be elevated, while if the chloride is 600 mg. per 100 c.c. or more the urea value probably will be within normal limits. Little advantage is to be gained by estimating the carbon dioxide combining power of the blood if the plasma chlorides are estimated, because the changes in the values of these two substances are in inverse ratio to one another.

In considering the advisability of the preoperative intravenous administration of fluids to patients suffering from pyloric obstruction it is wise not to be guided entirely by the values for various chemical factors in the blood, since dehydration and perhaps a deficiency of chlorides in the tissues may exist even in the presence of normal values in the blood.

Finally in treating the patient the physician can expect a rapid return of the abnormal values to normal levels if he administers sodium chloride,

d-glucose and fluid intravenously. The amount of these substances and fluid which must be given and the rapidity with which they can bring a return to normal values are roughly proportional to the degree of elevation of blood urea and the depression of the value for plasma chlorides.

Summary

A study has been made of the records of 151 patients suffering from gastric or duodenal ulcer or carcinoma of the stomach complicated by pyloric obstruction to determine the effect of certain factors which might account for the chemical alterations which occur in the blood of many such patients.

There is a positive correlation between the amount of vomiting and the decreased values for plasma chlorides, the increased values for blood urea, and the increased carbon dioxide combining power of the blood. We are unable to establish a definite relation between the values for these three chemical factors and the type of lesion present, the age of the patient, the amount of retained gastric content, the concentration of free hydrochloric acid in the gastric content, or combinations of several of these factors. The decreased values for plasma chlorides appear to be due in large part to loss of chloride as a result of vomiting but this is probably not the only factor involved.

Patients with achlorhydria as a rule show changes in the blood similar to those in patients suffering from pyloric obstruction in whom free hydrochloric acid is present in the gastric content. In patients in whom hemorrhage into the gastrointestinal tract occurs in association with pyloric obstruction the mean values for blood urea are greater than in the entire group while values for plasma chlorides are lower in these patients with bleeding than in those in whom bleeding does not occur.

Quantitative studies of the metabolism of sodium, chloride, nitrogen and bicarbonates as well as other factors will be required before it can be ascertained which of the various factors mentioned are responsible for the characteristic changes in the chemistry of the blood in cases of pyloric obstruction.

It is clearly established that the characteristic changes of the blood in patients suffering from pyloric obstruction are readily amenable in most cases to intravenous injections of physiologic solution of sodium chloride and of 5 or 10 per cent of *d*-glucose.

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THE INFLUENCE OF INTRAVENOUS GLUCOSE INJECTIONS ON ABNORMAL ERYTHROCYTE SEDIMENTATION SPEED IN RELATION TO ACTIVITY OF INFECTION *

By S. S. LICHTMAN, M.D., *New York, N. Y.*

SEVERAL factors are known to influence erythrocyte sedimentation rate. Most important among these are plasma fibrinogen and globulins. Variations in sedimentation rate have been correlated with changes in the plasma proteins.[1-7] The liver plays a rôle in the regeneration of plasma proteins [8, 9, 10] and this function is impaired by infection.[11-14] An underlying hepatitis was empirically assumed by Gram [15] to be responsible for abnormal rates under all conditions. The rôle of the liver as one of the factors influencing erythrocyte sedimentation was also suggested by Snapper.[16] In frank liver disease, however, consistent changes in sedimentation rate have not been observed.[17, 18] It appears that a possible relation between abnormal sedimentation speed of erythrocytes and altered liver function has not been investigated adequately so that it is impossible as yet to formulate a definite conclusion.

After fever and leukocytosis have subsided in patients with rheumatic fever and pulmonary tuberculosis, the rapid sedimentation rate has been regarded as the main criterion of continued clinical activity of the infectious process. On this basis alone further physical inactivity is prescribed. Whereas ordinarily the abnormal rate definitely indicates active disease, in an occasional case the persistently rapid rate may possibly be independent of activity of the original disease and actually depend on a secondary disturbance, possibly in liver function, with a resulting lag in the restoration of factors responsible for the normal rate of sedimentation.

With this in mind the influence of intravenous glucose was tested in subjects with unquestionable evidence of fully active infection and in those in whom abnormal sedimentation speed of erythrocytes persisted as the main clinical criterion of activity. The beneficial influence of glucose on liver damage is well established.

PROCEDURE

Two or three control determinations of the sedimentation rate were made by the Linzenmeier [19] or Cutler [20] methods. After the rate had become stabilized with minimal variations, glucose injections were begun. Twenty to 50 c.c. of 25 or 50 per cent glucose were administered intravenously, daily, for four or six days. On the alternate days, 24 hours after each injection,

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From the Medical Division, The Mount Sinai Hospital, New York, Service of Dr. George Baehr.

the sedimentation rate was determined. After the total number of injections had been completed, the rates were determined at two or three day intervals. Determinations were made in the forenoon following a light breakfast.

Results

Glucose produced no change in the increased sedimentation rates of two patients with suppurative bronchiectasis, one with Hodgkin's disease, and one with multiple myeloma (table 1).

Table I

The Effect of Intravenous Glucose on Erythrocyte Sedimentation Speed in Fully Active Disease and Infection. Multiple Myeloma; Hodgkin's Disease; Suppurative Bronchiectasis

Case No.	Diagnosis	Control (Before Injection) *Days*			Intravenous Glucose † *Days*			After Glucose *Days*		Clinical Notes
		6	4	2	2	4	6	3	6	
F. N. 1	Multiple myeloma	7*	12	8	5	12	10	15	10	Febrile severe anemia.
T. M. 2	Hodgkin's disease	11	15	—	12	15	17	15	15	Intermittent fever. Pulmonary lesion. Leukocytosis.
G. M. 3	A putrid lung abscess. Bronchiectasis	21	35	31	33	31	30	—	31	Low grade fever. Pus by bronchoscopy.
R. G. 4	Suppurative bronchiectasis	14	23	19	22	—	18	15	20	Subfebrile. Pus by bronchoscopy.

* Linzenmeier method: S.R. expressed in minutes (normal rate, 18 millimeters in 60–120 minutes).

† 20 c.c. of 50 per cent glucose.

Seven patients with rheumatic fever received intravenous glucose. In cases 5, 6, and 7, with fully active carditis, fever, leukocytosis and electrocardiographic changes, glucose exercised no influence upon the abnormal sedimentation rate (table 2).

In case 8 (figure 1) glucose did not affect the rate in two series of injections during two cycles of active rheumatic infection.

Glucose exercised a definite effect on sedimentation rate in two cases (9 and 10) of subacute rheumatic fever (figures 2, 3). In case 9, the rate was slowed from a sedimentation speed of 18 millimeters in 17 minutes to 18 millimeters in 35 minutes after two injections of glucose. This rate was maintained during the injections. It continued to slow, requiring 51 minutes to sediment 18 millimeters after discontinuation of the glucose injections. In case 10, the rate slowed from a sedimentation speed of 18 millimeters in 18 and 14 minutes, respectively, to 35 minutes after three injec-

TABLE II

Glucose Effect in Acute Rheumatic Carditis

Case No.	Diagnosis	Control (Before Injection) *Days*			Intravenous Glucose † *Days*			After Glucose *Days*			Clinical Notes
		6	4	2	2	4	6	2	4	6	
J. W. 5	Carditis Polyarthritis	—	—	30*	21	29	34	53	60+	60+	No leukocytosis. E.C.G.: P–R changes. Fever (101° F.).
I. P. 6	Carditis Arthritis	14	18	21	18	22	—	30	50	59	Leukocytosis (15,400 W.B.C.). Fever (102.8° F.).
L. B. 7	Carditis Polyarthritis	25	22	40	39	49	—	49	60+	60+	No fever or leukocytosis. E.C.G.: P–R changes.
H. B. 8	Carditis Erythema multiforme	24	21	20	20	24	—	32	44	36	See figure 1.

* Linzenmeier method: S.R. expressed in minutes.
† 25 c.c. of 25 per cent glucose.

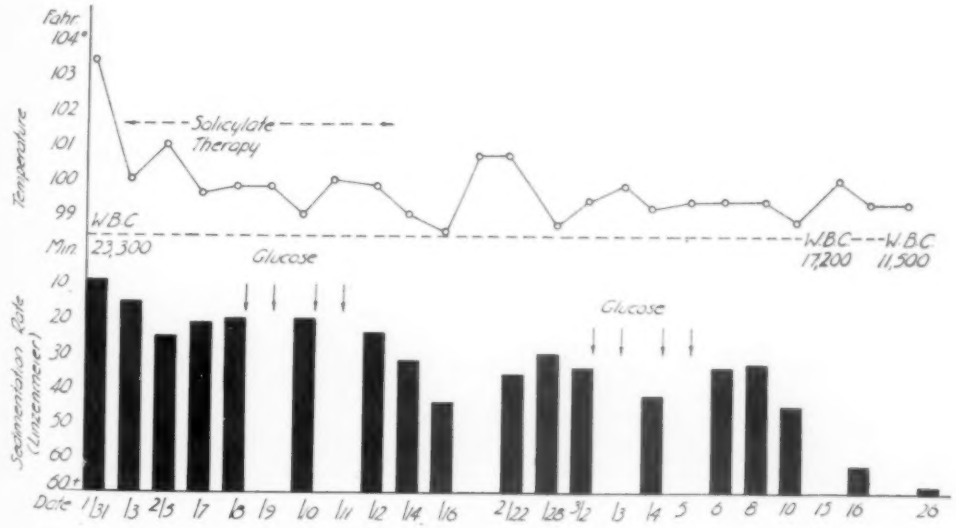

FIG. 1. (Case 8.) Acute rheumatic carditis. Erythema multiforme. Aged 13 years. Intravenous glucose without effect on sedimentation speed. Two courses of injections; 25 c.c. of 25 per cent glucose daily.

tions of glucose. This decreased sedimentation speed was maintained during the glucose period. Immediately thereafter, however, it returned to the more rapid pre-injection sedimentation speed of 18 millimeters in 18 minutes.

In the latter case the glucose produced a temporary effect, in the former a lasting effect.

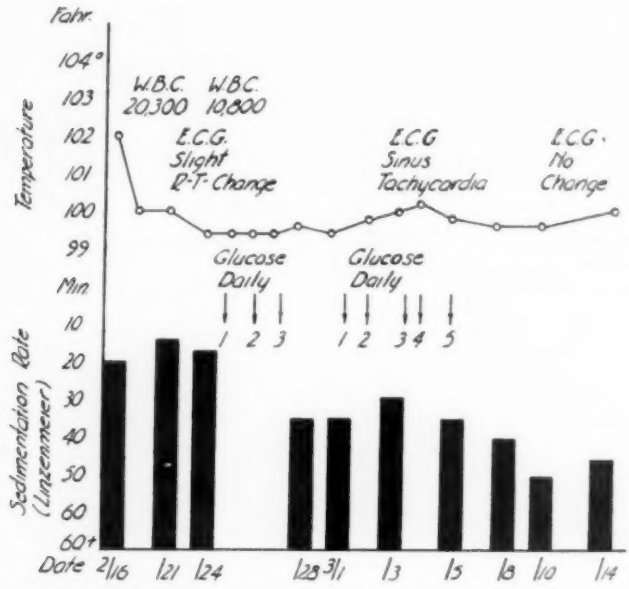

FIG. 2. (Case 9.) Subacute rheumatic carditis. Aged 14 years. Progressive slowing of sedimentation speed following both courses of intravenous glucose; 25 c.c. of 25 per cent glucose daily.

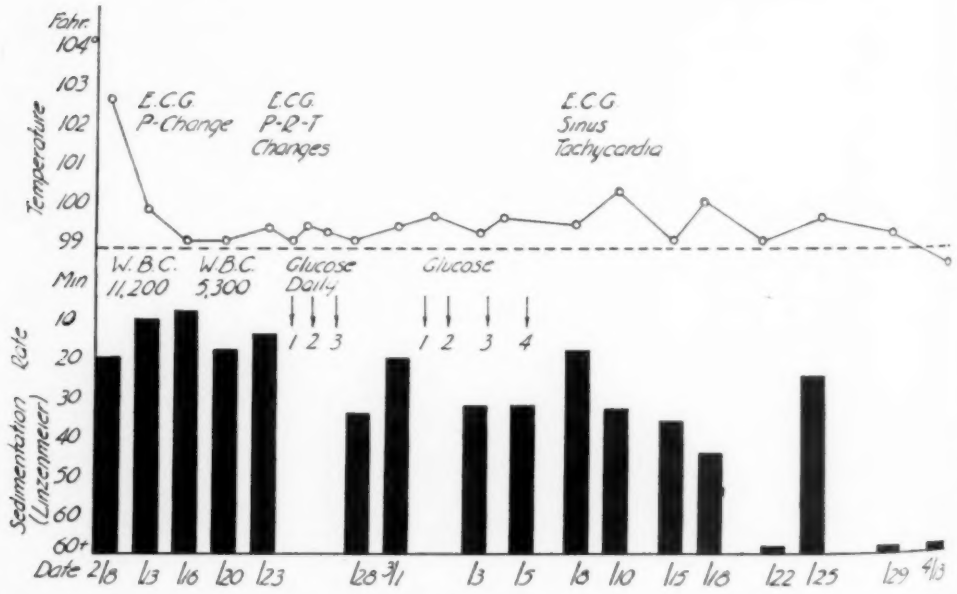

FIG. 3. (Case 10.) Subacute rheumatic carditis. Bronchopneumonia. Aged 14 years. Temporary slowing of sedimentation speed during intravenous glucose. Return to original rate after both courses of injection; 25 c.c. of 25 per cent glucose daily.

Nine patients with pulmonary tuberculosis received intravenous glucose (table 3). In three cases (cases 11, 12, 13) with fully active, febrile, moderately or far advanced tuberculosis of the lungs, glucose effected no change in the erythrocyte sedimentation rate. In two patients (cases 16, 17) with moderately advanced pulmonary tuberculosis, rated clinically inactive except for rapid sedimentation rates, glucose produced negligible changes in rate.

In the remaining four cases of afebrile, clinically inactive, moderately advanced tuberculosis definite effects were produced by glucose. In case 14 (table 3) there was a temporary retardation of the sedimentation speed of 20 and 22 millimeters in 60 minutes to 18 and 16 millimeters during the

TABLE III

Influence of Intravenous Glucose on Abnormal Sedimentation Rate in Patients with Fully Active and Clinically Inactive Pulmonary Tuberculosis *

Case No.	Control (Before Injection) *Weeks*		Intravenous Glucose § *Days*		After Glucose *Days*		Clinical Notes
	2	1	3	6	3	6	
J.L. 11	22†	22	22	22	22	—	Far advanced. Fever. Pulse rapid. Cavitation. Gaffky 6.
L. K. 12	28	29	27	26	27	—	Far advanced. Fever. Gaffky 7. Cavitation.
S. S. 13	32‡	25	28	30	29	—	Moderately advanced. Fever. Cavitation. Sputum negative. Artificial pneumothorax.
A. W. 14	20	22	18	16	20	20	Moderately advanced. Afebrile. No leukocytosis. Sputum negative.
M. B. 15	19	19	15	14	14	16	Moderately advanced. Small cavity. Afebrile. Pulse normal. Sputum negative.
E. de F. 16	24	23	25	22	22	24	Moderately advanced. Marked hypertension. Pulse and temperature normal. Sputum positive.
W. H. 17	20	21	20	18	—	—	Moderately advanced. Pulse and temperature normal. Sputum negative.

* Studies made on patients with pulmonary tuberculosis were made possible through the kind coöperation of Dr. Fred. Heise, Medical Director, and Dr. John Steidl, Resident Physician, The Trudeau Sanatorium, Trudeau, New York. Dr. Lee Lichtman, Summer Intern, made the injections and the determinations in these cases.

† Cutler method: sedimentation rate expressed in millimeters (normal 6–10 mm. in 60 minutes).

‡ Linzenmeier method: sedimentation rate expressed in minutes. Case 13 only.

§ 20 c.c. of 25 per cent glucose, daily.

period of glucose injections and a prompt return to a speed of 20 millimeters in 60 minutes after the glucose. In case 15 (table 3) the rate of 19 millimeters was slowed to 14 millimeters and remained at that rate after the glucose was discontinued. In case 19 (figure 5) normal sedimentation speed was restored during the glucose phase, but the original abnormal rate was resumed immediately afterwards. In case 18 (figure 4) the normal rate which had been restored by glucose from a rapid sedimentation speed of 20 millimeters in 60 minutes persisted after glucose. The abnormal rate had existed for several months prior to the glucose test.

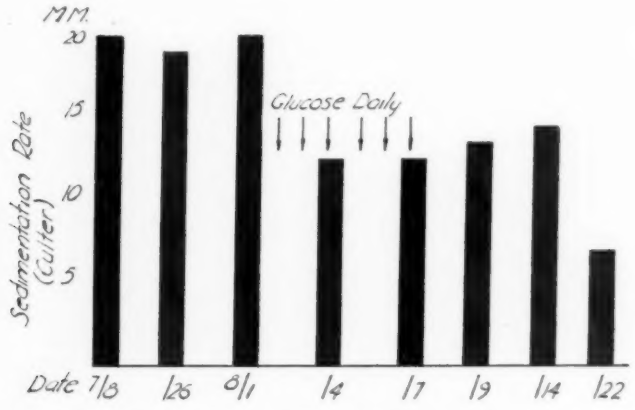

FIG. 4. (Case 18.) Moderately advanced pulmonary tuberculosis, pulse rate normal. Afebrile. Sputum positive. No cavitation. Complete restoration of normal sedimentation speed of erythrocytes during and after glucose administration; 20 c.c. of 25 per cent glucose daily.

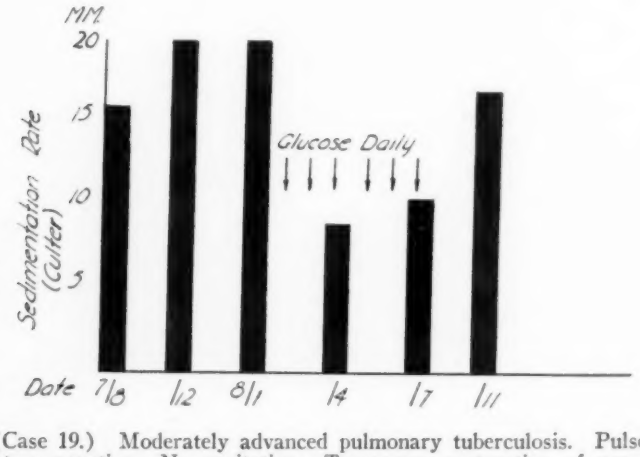

FIG. 5. (Case 19.) Moderately advanced pulmonary tuberculosis. Pulse rate normal. Afebrile. Sputum negative. No cavitation. Temporary restoration of normal sedimentation speed during glucose administration; 20 c.c. of 25 per cent glucose daily.

Comment

The slowing of the erythrocyte sedimentation speed noted in some instances after the intravenous injection of single daily doses of glucose cannot be attributed to the direct action of the sugar upon the circulating blood, since the readings were made 24 or more hours after the injection. On the contrary, the direct addition of glucose to an erythrocyte suspension has been demonstrated to accelerate sedimentation.[21] It is also improbable that the injected glucose directly affected the focus of infection itself histologically or immunologically. It is believed that the retarding influence of the intravenous injection of glucose on the rapid sedimentation speed of erythrocytes in some instances may depend upon the beneficial effect of glucose upon liver function in its relation to plasma protein regeneration but no direct evidence is presented to prove this hypothesis.

Liver function disturbances have been noted in rheumatic fever and in pulmonary tuberculosis.[22, 23] It is uncommon to find a normal sedimentation speed in active pulmonary tuberculosis whereas it is not uncommon to find a normal sedimentation rate in active rheumatic fever. It cannot be stated at present whether this latter unexpected finding can be explained on the basis of undisturbed liver function.

The converse may also be true. The persistence of a rapid sedimentation rate after the apparent subsidence of an infection, as in pharyngitis, tonsillitis, etc.[24] does not necessarily signify, as has been stressed, that the focus of infection is still active. There may be a lag in the restoration of the factors responsible for normal sedimentation rate after the original focus of infection has subsided.

In seven of 19 cases with abnormal sedimentation rates intravenous glucose injections definitely influenced the speed in the direction of slowing. In no case did the glucose produce a slower rate during the injection period if the abnormal rate was accompanied by fever or leukocytosis during that period. The retardation of the sedimentation speed occurring during glucose injections was usually temporary, the original sedimentation rate reverting after the injections. In one instance, in a case of moderately advanced tuberculosis (case 18) without fever and leukocytosis for several months, a normal sedimentation speed was promptly restored during the glucose injections and persisted afterwards.

On the basis of the remarkable effect of intravenous glucose on repair of liver damage, it is suggested that the slowing of the sedimentation rate, after its injection in certain patients with infections and abnormal sedimentation speeds, may possibly occur through improvement of liver function. It is fully recognized that sedimentation speed of erythrocytes is influenced by numerous other factors, known and unknown. It is suggested, however, that hepatic injury through infection may be a special factor in certain instances where abnormal sedimentation speed persists after other clinical criteria of infection indicate inactivity of infection. Under these circum-

stances intravenous glucose injections may serve promptly to restore normal sedimentation rates.

Summary

Daily intravenous glucose injections administered to 19 subjects with various types of disease and infections, including rheumatic fever and pulmonary tuberculosis, marked by abnormal erythrocyte sedimentation speed, *slowed* the sedimentation rate in seven during the period of glucose injections. *The slowing effect of the glucose was not noted if fever or leukocytosis accompanied the abnormal sedimentation speed during the period of glucose injections.*

Among numerous other factors influencing sedimentation rate, liver damage through infection and disease may in some instances influence the sedimentation speed of erythrocytes. It is suggested that intravenous glucose may serve to correct such factors although no direct evidence in support of this hypothesis is as yet available.

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ARSPHENAMINE POISONING WITH REPORT OF FOUR CASES *

By Gerald C. Parker, M.D., and Orman C. Perkins, M.A., M.D., F.A.C.P., *Brooklyn, New York*

Previous reports concerning the toxicity of arsphenamine have described effects ranging in severity from local skin reactions to sudden death. In a recent contribution by Globus and Ginsburg, the literature has been very ably reviewed. They advance their theory as to the pathological process for which they propose a new name, "pericapillary encephalorrhagia." The pathogenesis of this process has received much consideration from others, notably Oliver and his co-workers, whose description of experimental lesions is the basis of our observations.

Joseph and Fleig showed that acid arsphenamine produced reactions due to intervascular precipitation which did not occur with alkaline disodium arsphenamine. Hanzlik and Karsner first demonstrated the agglutinating action of arsphenamine on the red blood cells. Oliver and Yamada described the early and the late toxic reaction of arsphenamine. The early reactions were due to agglutination of red blood cells resulting in embolism with the clumped cells. Late effects, such as nephritis and atrophy of the liver, do not occur as the result of embolism with agglutinated cells but are due to the chemical toxicity of the constituents of arsphenamine.

In the administration of arsphenamine, agglutination is prevented by the addition of some colloid such as gelatin, gum acacia, egg albumin and protein from blood plasma. These substances influence the action of arsphenamine on the red blood cells by preventing its absorption, with resulting agglutination and embolism. Oliver later demonstrated that this protection is due to the union of the arsphenamine with the colloids and not with the red blood cells. He further found that if the dose is greatly increased, thereby saturating the blood plasma, the excess of arsphenamine is then present in the red blood cells and agglutination and embolism occur.

Case Reports

Case 1. M. P., a white woman, aged 24, housewife, Italian, had been treated in the hospital dispensary during June 1931. The family history was negative, as was the history of previous illnesses. Menstrual periods had been regular without pain. The husband had been treated for syphilis 11 years before for a period of only two weeks. The patient did not know she had syphilis until a Wassermann test was made in the clinic. She had been married 11 years. She had been four times pregnant, but there was some discrepancy in the obstetrical history for it was said she had one living child and two miscarriages.

On June 28, the patient visited the clinic and received her second intravenous injection of arsphenamine. She did not feel well following this and had rather vague

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pains. On June 30, the patient was visited by her sister until about 3 p.m. and at that time she had only a few vague complaints. Her husband arrived home about five o'clock and found her sitting in a chair looking into space. She was unable to talk or to move her legs although she could move her arms. There was a tendency toward flexion at this time. She was seen by her doctor and later was admitted to the hospital on the service of Dr. Warren.

When examined she did not appear to be acutely ill, although she did not talk and was unable to coöperate. Her eyes were wide open, but she apparently was not aware of her surroundings. Her face was flushed and expressionless. There was neither nausea nor vomiting and she did not appear to have headache. Temperature was 101° F., pulse 120, respiration 22, systolic blood pressure 120, diastolic 90. The head showed no signs of trauma. The eyes reacted to light; there was a coarse nystagmus to the right and internal strabismus of the left eye. Corneal reflexes were present. The lips were very dry, and the patient resisted oral examination. The neck was not rigid and exhibited no unusual glands. The lungs and heart were normal. The arms were spastic, the fingers flexed but could be extended. The reflexes were equal and there was no evidence of paresis or paralysis. The legs were flaccid but not paralyzed, and the reflexes were normal.

Laboratory findings: red blood cells 4,250,000, white blood cells 8,400, hemoglobin 82 per cent, polymorphonuclear neutrophiles 76 per cent, eosinophiles 2 per cent, small lymphocytes 24 per cent, and large lymphocytes 4 per cent. The blood Wassermann test was equivocal. Cerebrospinal fluid obtained by a cisternal puncture contained 360 cells per cu. mm., polymorphonuclear neutrophiles 50 per cent, large lymphocytes 50 per cent. The fluid contained globulin. Urinary examination was negative. The blood sugar was 135 mg. per 100 c.c., chlorides 644 mg. per 100 c.c., creatine 1.5 mg. per 100 c.c.

While under observation the coma seemed to deepen, the respirations became more rapid and shallow, and there was cyanosis of the lips. The pupils were contracted and there was lateral nystagmus more to the left. When stimulated the arms flexed with a fine clonic form of contraction. The skin was flushed and perspiration was very free. Pregnancy was revealed by fetal heart sounds. The temperature continued to run a septic course until on August 3 it went up to 106° F., and the patient died.

Necropsy: Gross Findings: The brain before fixation was extremely soft. The convolutions were flattened and the sulci narrowed. The pial blood vessels over the cortex and at the base were markedly congested, but there was no evidence of hemorrhage. The corpus collosum was ruptured due to handling, and there could be seen a large discolored area below. Examination of the brain after fixation in 10 per cent formalin did not show any gross abnormalities. On sectioning the gray matter was easily distinguished from the white matter. The discoloration appeared to be confined to the white matter extending from the mid-frontal region anteriorly to the tip of the occipital lobe posteriorly, including the basal ganglia, pons, and the cerebellum (figure 1). There was no involvement of the medulla. The ventricles did not show any undue dilatation.

Microscopic Examination: Sections were taken from various parts of the brain, including the discolored area, and a number of stains were made including hematoxylin-eosin, toluidine blue, Weigert-Pal, Bielchowsky, Giemsa and the Hortega-Globus modification. With the low power the pia was markedly thickened, with an infiltration of cells in the meshes of the pia, and a few blood vessels showed perivascular infiltration. With the high power the infiltrating cells were seen to be lymphocytes. The blood vessels were congested, their walls were slightly thickened and there was a perivascular infiltration of lymphocytes. In the gray matter of the cerebral cortex the ganglion cells were in a good state of preservation. There was a

moderate degree of gliosis, mostly of astrocytes and oligodendroglia (figure 6). The blood vessels in the gray matter were slightly thickened and a few showed perivascular infiltration of lymphocytes. There were no areas of hemorrhage seen in the gray matter. In the white matter, particularly in the discolored area, there were numerous ring-like hemorrhages, which varied in size and number, but were present

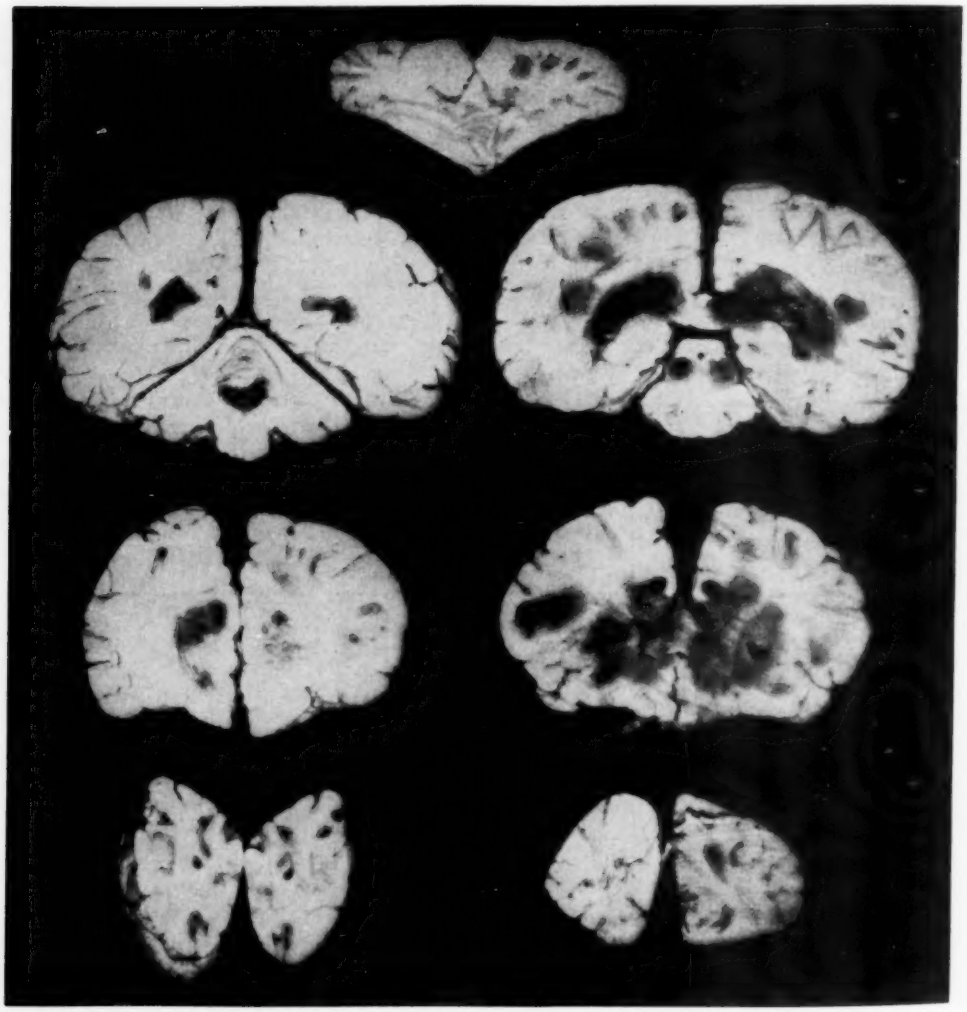

FIG. 1. The gross appearance of hemorrhages, extending from the mid-frontal region to the mid-occipital region and including the pons and cerebellum.

in all sections (figures 2 and 3). In some of these ring-like hemorrhages a central blood vessel could be seen, which in some cases was ruptured (figure 5). Around the blood vessel could be seen an area of demyelinization around which was a dense ring of extravascular blood. About the latter there was a gliosis, mostly astrocytes and oligodendroglia, which extended into the tissue. In all sections from areas where this discoloration was seen in the white matter these characteristic ring-like hemor-

rhages were observed. In brief, the lesions described here are extravascular hemorrhage with rupture of the blood vessel wall, and moderate gliosis of astrocytes and oligodendroglia.

Case 2. A. M., a white man, aged 41, was admitted to the Kings County Hospital on January 22, 1934. He was comatose, but made aimless movements with his arms. His skin was moist and his breathing was labored. About every 15 to 20 minutes he would cry out and there would begin a series of clonic convulsive move-

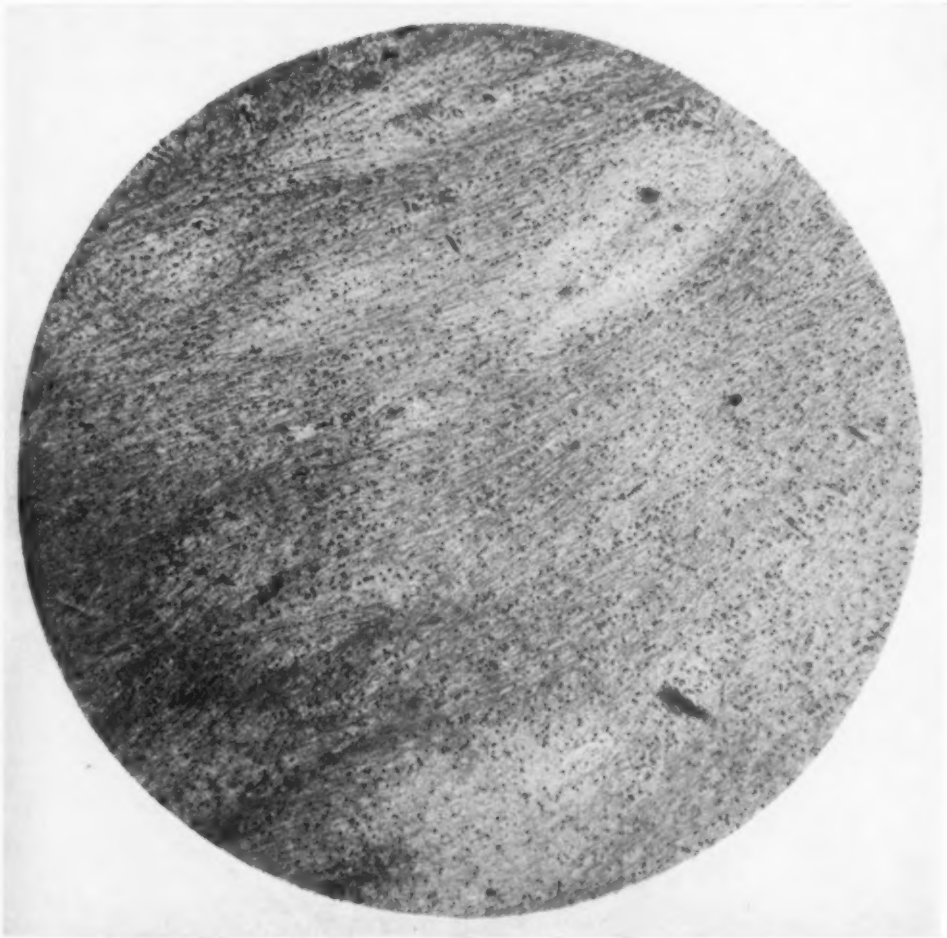

FIG. 2. Microscopic appearance under low power showing light areas around thrombosed blood vessels. Hematoxylin-eosin × 70.

ments of both arms and legs which seemed to have the same amplitude and force on one side of the body as on the other. The head would turn to the right and there was conjugate deviation of the eyes to the right. The pupils were contracted, but there was a slight reaction to light of the right pupil, none of the left. The conjunctivae were injected. All the deep reflexes were hyperactive but equal. There was a bilateral Babinski reaction, but no ankle clonus. These convulsive seizures would last for a few minutes and then the patient would relax.

A spinal tap yielded blood tinged spinal fluid with a pressure of 22 mm. of mercury. It contained globulin (+++) and gave a paretic colloidal gold curve. Both blood and spinal fluid Wassermann reactions were strongly positive. The patient died eight and a half hours after admission to the Hospital. During this time his temperature ranged from 98.4° F. to 100° F., and his pulse from 100 to 120. Systolic blood pressure was 130, diastolic 80.

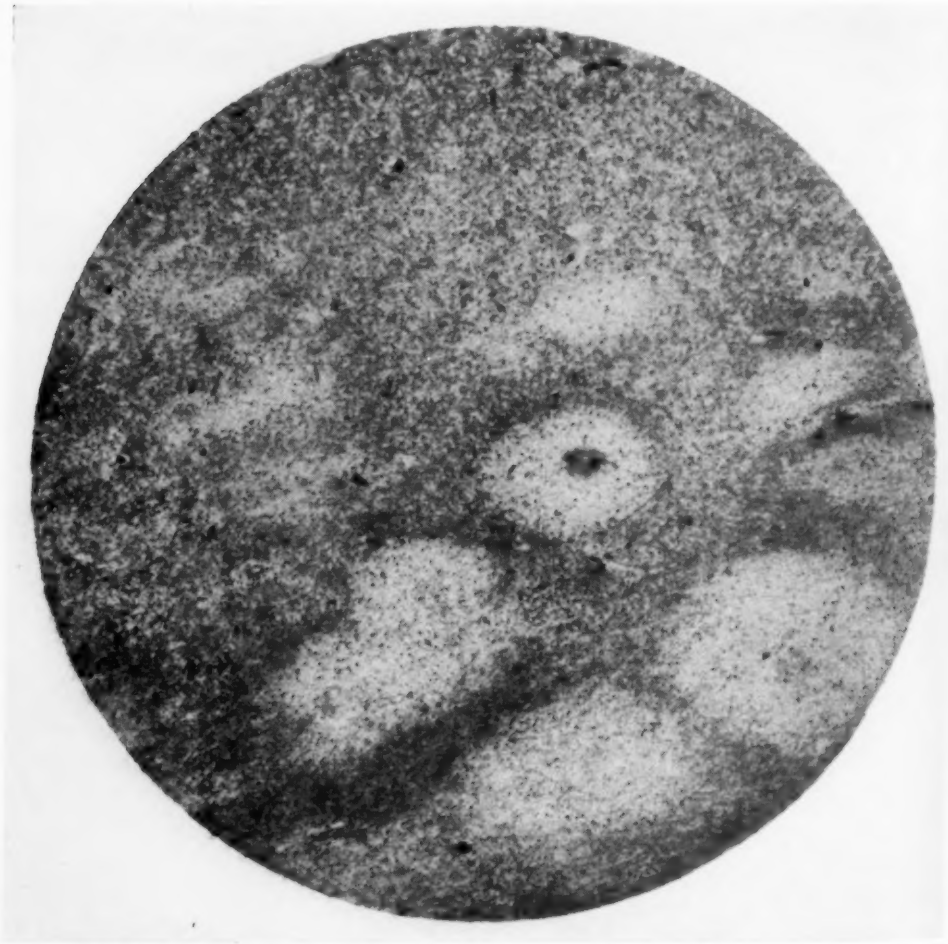

FIG. 3. Microscopic appearance of hemorrhage under low power showing numerous demyelinized areas around thrombosed blood vessels. Weigert-Pal × 70.

The necropsy showed the dura mater to be under tension. The convolutions of the brain were flattened, the sulci were obliterated and the blood vessels were congested. The brain weighed 1450 gm. The ventricles were dilated and contained blood tinged fluid. The stained sections of the brain showed the typical microscopic picture of arsenical encephalitis. Examination of the other organs showed chronic myocarditis, luetic aortitis, congestion of the spleen, chronic vascular nephritis, and chronic hepatitis.

It was possible to obtain a history from the physician who was called in at the onset of the convulsions. This patient had been receiving injections of arsphenamine and the latest injection was 18 hours before the unheralded generalized convulsion.

Case 3. E. C., a white man, aged 33, was admitted to the Kings County Hospital on January 30, 1934. The day before he had remained at home because of severe headache, and the following morning while walking to the bathroom he collapsed. He was not unconscious, but was unable to get to his feet. Several hours after he

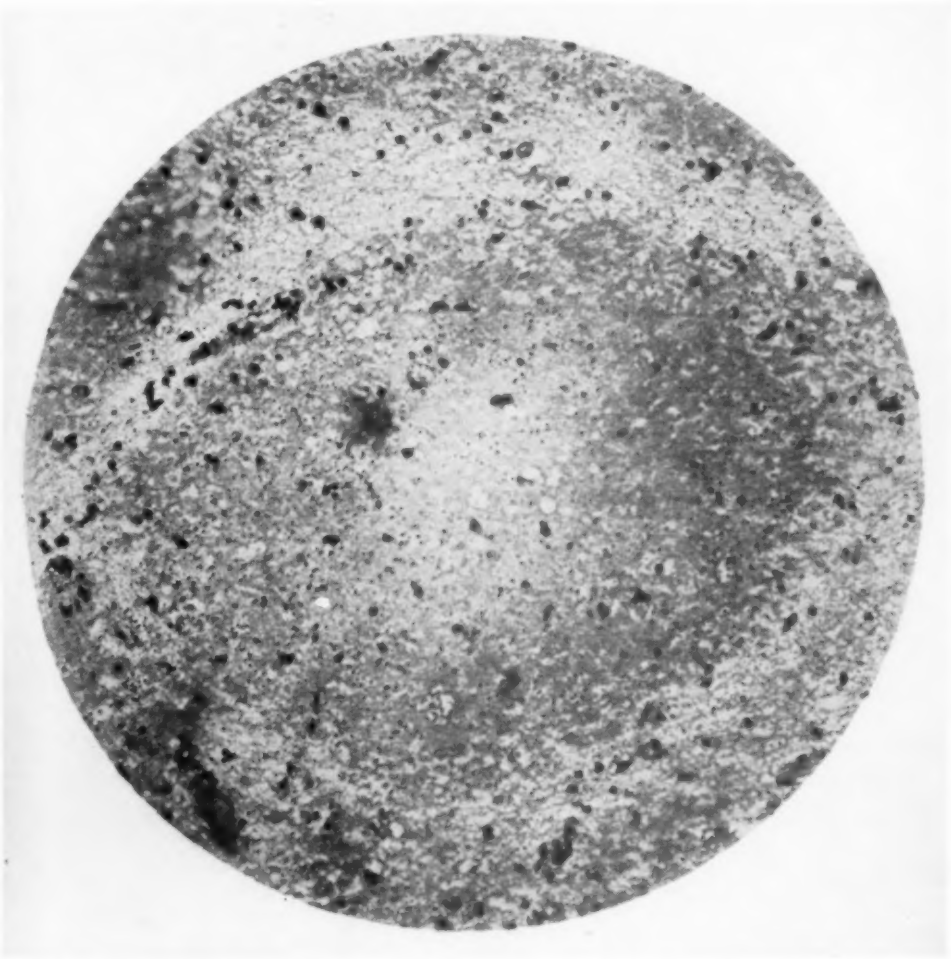

FIG. 4. An individual ring hemorrhage with central arteriole. Hematoxylin-eosin × 300.

had been put to bed he became stuporous, began to scream and seemed to be choking. This was followed by convulsions.

On admission to the hospital, the patient was in coma. His face was flushed, the breathing was stertorous, and he was incontinent. The pupils were irregular, but reacted to light. The disc outlines were clear and the retinal vessels appeared normal. There was difficulty in opening the mouth, on which was dried blood from biting the

tongue. There was no rigidity of the neck. All the deep reflexes were active and equal. Bilateral Babinski response and ankle clonus were present. The spinal fluid pressure was 36 mm. of mercury, and the fluid was bloody.

The following morning the patient was stuporous but could be aroused. He talked rationally and recognized his relatives. He denied ever having had a venereal disease or that he had received injections of any kind at any time. The examination of the blood showed a white cell count of 9,450, with 69 per cent polymorphonuclear leuko-

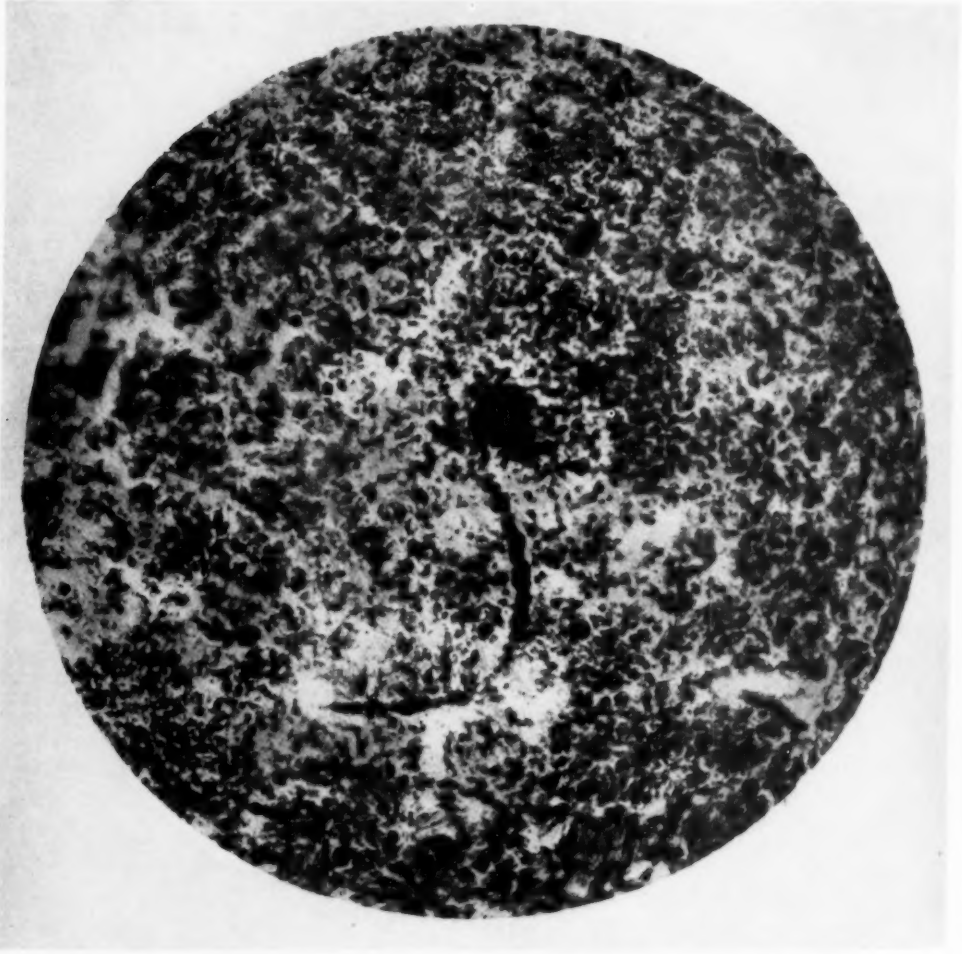

FIG. 5. A ring hemorrhage showing a central vessel which has ruptured with blood vessel leading to it. Hortega silver carbonate stain × 300.

cytes. The clotting time was five and a half minutes. The blood Wassermann test was strongly positive. The blood urea was 35 mg., creatine 1.22 mg., and sugar 88 mg. per 100 c.c. The urine, spinal fluid, hair and nails were examined for arsenic which was found in the urine and nails. When the patient was told the result of the Wassermann test and that arsenic had been found in his urine and nails, he admitted that he had syphilis and had been receiving treatment for the disease. He had his last injection of arsphenamine two days before his admission to the hospital.

The temperature on admission was 101° F., and ranged between 101° F. and 102° F., until the fifth day when it reached 103° F. On this day râles and definite evidence of lobar pneumonia were found in the right lower lobe. These signs disappeared in six days, but the temperature continued to range between 100.4° F. and 101.8° F., until his death on the seventeenth day in the hospital.

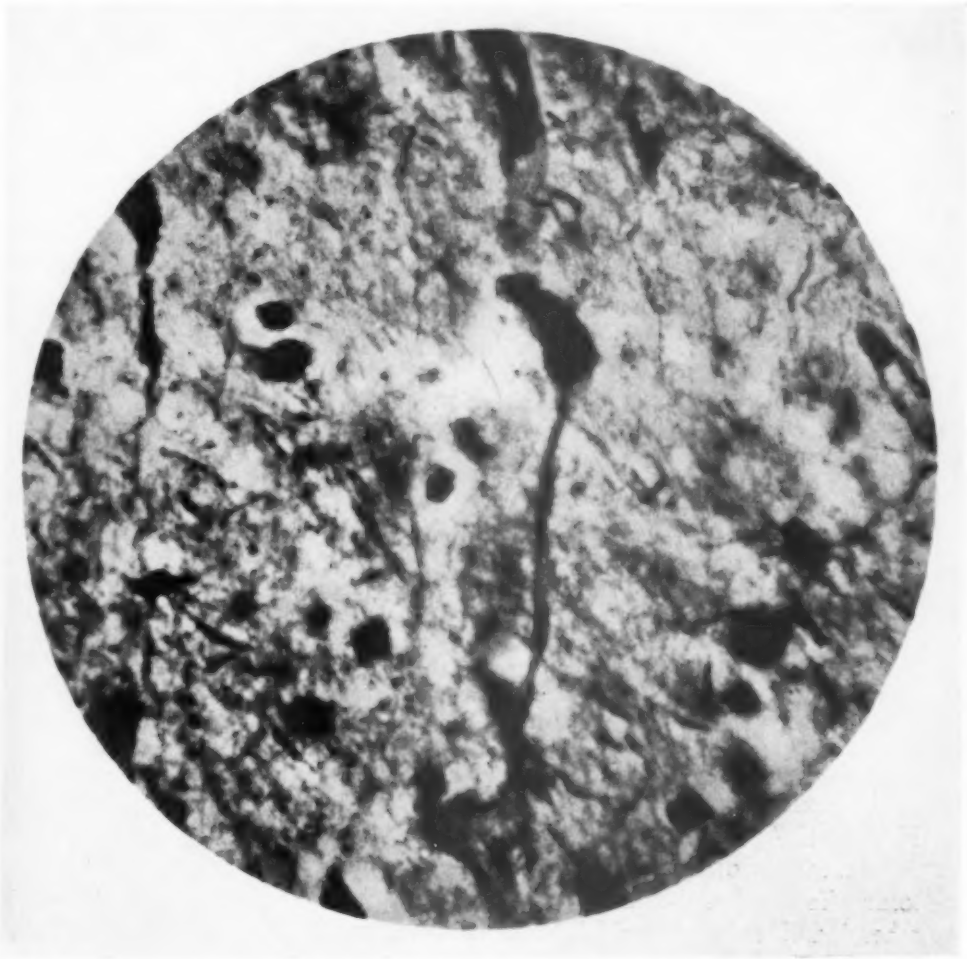

FIG. 6. Oligodendroglia cells undergoing degenerative changes × 600. Globus modification of Hortega silver carbonate stain.

After regaining consciousness on the second day, he remained rational until the ninth day. During this time he gradually became deaf. He was drowsy and took very little interest in what was going on about him. In the second week he became very restless during his short waking periods. He was irrational. There were no other cranial nerve palsies and no weakness noted in his extremities. He developed tremors in the arms which continued for four days to within a few hours before his death.

At necropsy there was no evidence of pneumonia. The heart was somewhat increased in size, and the myocardium edematous and swollen. The liver showed a slight increase of fibrous tissue and its sinuses were filled with blood. The spleen was normal in size, dark slate in color. It also showed an increase of fibrinous tissue stroma. The kidneys appeared normal. There was a marked pial and subpial hemorrhage extending into the brain substance. The hemorrhage and softening involved the periphery of both cerebral and cerebellar hemispheres and scattered areas of somewhat symmetrical distribution. The stained sections of the brain tissue showed the typical picture previously described of arsenical encephalitis.

Case 4. J. P., a white man, aged 36, was seen in his home on March 16, 1934. His family stated that he had been receiving injections for syphilis at a clinic and that he had had his last treatment the day before. He had been working for weeks and had no complaints. He slept well the night after the last injection, but awoke with such a severe headache that he did not go to work. He remained in bed, and at 10 o'clock had his first convulsion. He did not lose consciousness but continued to have convulsions every 15 to 30 minutes. He became irrational, screaming, and it was necessary to hold him in bed. After several of these attacks it was noted by the family physician that there was weakness of the entire left side of his body.

When examined, seven hours after the onset, the patient was irrational, noisy, and extremely restless. The disc outlines were clear. The pupils were equal and reacted to light. There was a paralysis of the left side of his face, his left arm and left leg. The blood pressure was 118 systolic and diastolic 78. The temperature was 100.8° F.; the pulse 120. The patient was admitted to the Kings County Hospital. On the second day after admission to the hospital the convulsions stopped. The spinal fluid was blood tinged and under 24 mm. of mercury pressure. The spinal fluid and blood Wassermann reactions were strongly positive. Arsenic was present in the urine.

For eight days the patient was stuporous, but could be easily aroused. When aroused he was irrational and at no time recognized his relatives. The second week he became more restless and noisy, and on the eighteenth day he was committed to the State Hospital for the Insane. At the time of his commitment he had regained much of the use of his left arm and leg and his general physical condition was very good. I have followed the course of this patient in the State Hospital up to the present time. He has shown progressive deterioration mentally, although his physical condition still remains fairly good. He has almost full use of his left arm and leg.

Each of these cases demonstrates somewhat different points of interest in the toxic effects of arsphenamine. The first patient was pregnant, and Plass and Woods [6] have emphasized the point that, from their experience and from a review of the literature, pregnant women are more susceptible to the toxic effects of anti-syphilitic treatment by the modern arsenicals than are other individuals. Pritzi [7] believes that this susceptibility increases as term is approached.

The second case illustrates a clinical picture which, with the additional finding of blood in the spinal fluid, is frequently diagnosed subarachnoid hemorrhage. Many errors have probably been made in the diagnosis of such cases. The symptoms in our case appeared 18 hours after the injection and the patient died in less than 10 hours after the onset.

The third case illustrates the typical type of onset and the subsequent clinical picture, but here there was a prodromal symptom of headache preceding the collapse. These prodromal symptoms have been noted in several cases and although headache is the most consistently present symptom, men-

tal confusion seems to occur quite frequently. A recent patient in the Long Island College Hospital was confused for several hours prior to the attack, but was able to be up and was sweeping the sidewalk at the time of his collapse. This third patient denied having had syphilis or treatment for the disease, and although the clinical picture was typical of arsenical encephalitis the history of this case proves the necessity of a chemical analysis of the body tissues or excretions to establish the diagnosis. In this case the patient recovered from the acute onset and appeared to be improving, but after a few days he began to show a progressive mental deterioration which continued to the time of his death.

The fourth patient presented the typical type of onset with severe headache preceding the convulsion. In this case we have the neurological findings indicating localized brain damage. Although the general condition of this patient improved after his admission to the hospital, there was no improvement in his mental state and he shows progressive mental deterioration at the present time.

Our explanation for the pathological process is based on the several findings of Oliver and his co-workers, and those of Hanzlik and Karsner. The latter authors were the first to describe the agglutinating action of arsphenamine on red blood cells and later Oliver and Yamado demonstrated the agglutination of red blood cells, when placed on a slide after the administration of arsphenamine, and the formation of emboli in the brain and other special organs. Oliver also showed that the systemic blood pressure was first lowered after the administration of arsphenamine and that this fall is succeeded by a rise in blood pressure.

On this evidence is based our hypothesis that in the administration of acid arsphenamine there is first an agglutination of red blood cells which results in minute emboli in the vessels of the brain and other special organs. The blood pressure after the administration of arsphenamine is first lowered, but later elevated. The embolized and possibly weakened blood vessels may rupture in the stage of elevated pressure. This train of events seems to us to best explain the occurrence of the ring-hemorrhages.

The statistics of Cole [8] and his collaborators show that those patients who have latent syphilis are more apt to develop reactions than are those with early lesions. These authors also believe that young adults are more susceptible to the toxic effects of arsenical injections. Our experience with these cases leads us to hold the same opinion, and we wish to offer a word of caution in the use of arsphenamine in latent syphilis, especially in cases of pregnancy or where there is evidence of central nervous system invasion.

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ARTHRITIS—A NEGLECTED DISEASE*

By R. Garfield Snyder, M.D., F.A.C.P., *New York, N. Y.*

Although it is increasingly evident that people are becoming more conscious of rheumatic diseases, and particularly arthritis, there still exists a woeful apathy and lack of accurate knowledge regarding these diseases, not only from the medical point of view but from the sociologic aspect as well.

It will probably be a distinct surprise to most readers to learn that an exhaustive national health survey [1] made in 1935–1936 by the United States Public Health Service, disclosed that among chronic diseases in the United States, "Rheumatism" ranks first in prevalence, second in producing disability and second in producing invalidity. While only fourteenth in causing death, rheumatism was found to produce more invalids than did heart disease and twice as many as all types of tuberculosis. More important, it led all other diseases, even heart disease, in duration.

The survey further showed that among the 127,000,000 persons in the United States, there are 6,850,000 cases of rheumatic diseases, 3,700,000 cases of heart disease, 930,000 cases of cancer and other tumors, 680,000 cases of tuberculosis in all its forms, and 660,000 cases of diabetes.

The significance of these figures cannot be minimized by suggesting, as many people believe, that most cases of rheumatic diseases occur in persons of advanced age. In fact, 50 per cent of the surveyed group were under 45 years of age and half of those permanently disabled were under 55 years of age.

The term "Rheumatic Diseases" is an all-inclusive one covering an almost unlimited number of variations, but in general the term is accepted to include any disease causing ache or pain in the ligaments, muscles or joints. Rheumatic diseases are known to be the oldest of which the world has any record. Indications of definite changes in the bone structure in and around the various joints, corresponding to what is today readily identified as osteo-arthritis, are apparent in the bones of Egyptian mummies. While they are most prevalent in those territories where dampness and cold prevail, they are not necessarily confined to any particular climate or section and as a group they play no favorites as to age, sex or type of individual. Thus, in children, we usually find acute rheumatic fever and a rarer type of arthritis known as "Still's" disease; as a rule, in the young adult up to 40, we may find various types of infectious arthritis (general and focal), and more often the dangerous and more crippling rheumatoid type; osteo-arthritis and gout are usually found in short, stout people past middle age, and still another variety, traumatic arthritis, is found in any type but usually it occurs in

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persons whose vitality happens to be temporarily or permanently at a low ebb, and is frequently common following a fall, injury or athletic strain.

Since it would be impossible to discuss the medical and sociologic aspects of the entire rheumatic disease group in a paper of this kind, consideration herein will be given only to certain forms of arthritis. In general, the various forms of this particular disease are more painful, last longer, are more difficult to treat and, when especially severe, are apt to cause more permanent invalidity.

A breakdown of such reliable statistics as the writer has been able to gather indicates that of the total number of 6,850,000 persons suffering from rheumatic diseases throughout the United States, over 3,000,000 (mostly adults) have arthritis. About 130,000 of these are completely disabled and consequently represent a total loss of some 45,000,000 work days of earning power; there are 800,000 partially disabled victims, of which over 50 per cent are estimated to lose an average of five months' work (approximately 60,000,000 work days) out of the year. Therefore, more than 100,000,000 work days are lost by completely and partially disabled victims combined. Reckoning this time at a minimum average of $3.00 per day, we arrive at a wage loss alone of $300,000,000 per year, exclusive of cost of diagnosis and care.

In the presence of such evidence of its importance, it is almost inconceivable how arthritis continues to be the most ignored and neglected of all chronic diseases, by the medical profession and laity alike. It is clearly entitled to be termed "Medicine's Neglected Stepchild."

From the medical standpoint, it is obvious to anyone interested in this subject that one of the main reasons for such neglect is the marked lack of knowledge of arthritis or of interest in this disease among general practitioners. The belief seems to be widespread throughout the profession that it is a progressive and incurable disease and that consequently any attempt at therapy would be a waste of time and effort on the part of the physician and of money on the part of the patient.

In answer to the first part of such criticism, i.e., that the disease is a progressive and incurable one, it is the opinion of those authorities who have been especially concerned with the treatment of arthritis for many years, that at least 75 per cent of all cases can be cured or greatly improved if properly diagnosed and treated during the first year of incidence. About 50 to 60 per cent might be cured or materially helped when attended during the second and third year. Naturally, the earlier a case comes to the attention of the qualified physician, the better are the chances for the normal resistance powers of the individual to play an important rôle in recovery. On the other hand, just as in any other chronic disease, the longer the duration, the greater and more serious its cumulative effects on the general systemic condition of the individual and the lesser the chances of successful cure or improvement. Nevertheless, unlike the almost inevitable fate of a long-suffering tuberculosis or cancer patient, any of the leading authorities of

today can produce case histories to prove that even in longstanding, apparently hopeless cases, rehabilitation sufficient to return the victim to his former gainful occupation is often possible.

Specific data as to exact results and percentage of cures effected in this country are not available because as yet it has not been possible for all our hospitals and clinics to establish generally satisfactory follow-up systems, a condition which to a great extent is due to a peculiar reticence on the part of the patients. Except for a most exhaustive and complete effort to follow the clinical and life course of a large group of arthritis patients made by Dr. H. A. Nissen at the Robert Breck Brigham Hospital of Boston during the period from 1914 to 1934,[2] whatever statistical data the writer could find were largely representative of results obtained by physicians in private practice.

The results of Dr. Nissen's study disclosed that while from 15 per cent to 20 per cent of all cases of arthritis are apt to take a progressively backward course despite any and all forms of treatment, "in any group of so-called arthritics, *68 per cent or more can be assured of improvement.*" *

Furthermore, statistics from Sweden are very complete in this respect. There the care of the chronic rheumatism patient has developed to a most advanced stage. Nine free hospitals of some 60 beds each are devoted exclusively to their treatment. Cases are closely followed up sociologically for long periods after patients are discharged. The Swedish figures indicate that three years after discharge, 60 per cent of the patients are working at their former occupations and a further 18 per cent have been rehabilitated to such an extent that they require no further social aid.

While the criticism as to the futility of any attempt at therapy has been partly answered by the preceding statistics as to curability, the following might assist in further clarifying the subject and dispelling existing doubts as to the nature and value of treatment.

The term "arthritis" embraces a certain group of rheumatic diseases in which the most evident symptoms appear in the joints. In general, the various types of arthritis can be classified into two main groups, i.e., those of which the causative agent is known and those in which the exact causative agent has never been determined.

Whether the type is of known or unknown origin, one cannot overemphasize the need for early and accurate classification of all arthritis cases, together with prompt and appropriate treatment, which usually should include complete mental and physical rest if at all possible, and relief from the worry of financial obligations. Temporary cessation of occupation is often desirable and frequently vital.

Since optimum results can be obtained only by the efficient application of such medical and physical measures as are known to be of value, it should be obvious that prolonged and careful study must be given by any physi-

* This group is being followed to date. The results of the 1935 to 1938 follow-up have not as yet been published.

cian to acquire the ability, judgment and experience necessary properly to segregate and classify cases and equip himself to cope effectively with those that present unusual characteristics or require extraordinary measures.

The forms of arthritis of known origin comprise only about 25 per cent of the total number of cases, and the number of these with which any doctor is likely to come in contact, either in office or clinical practice, is extremely limited. Inasmuch as they can usually be solved by the application of accepted forms of specific treatment, they do not present particularly difficult problems. The remaining 75 per cent of all cases fall into the group of unknown origin which includes rheumatoid arthritis, infectious arthritis—either focal or general—osteo-arthritis, and gout. All of these types are extremely variable in nature and, with the exception of gout, no specific form of treatment can be prescribed for them.

From the layman's point of view, the apathy and neglect can be attributed to several factors, chief among which has been the lack of education and publicity regarding the possible dangerous implications of such common complaints as the growing pains of children, the repeated muscular pains, undue fatigue and general feeling of lassitude of the young adult, or the stiffening and aches in the joints of the elderly. Any or all of these manifestations might well be definite early symptoms of a serious type of arthritis which, just as in tuberculosis and cancer, should be attacked in their earliest possible stage of development.

Whether unwittingly or by necessity, many people either neglect such potential early symptoms or futilely try to doctor themselves, often with the aid of questionable "quack" methods, "short-cut" cures, patent medicines and home diathermy.

A survey of chronic diseases in the State of Massachusetts [3] made by G. H. Bigelow and H. L. Lombard in 1931, showed that of the total number of 140,000 persons suffering from chronic rheumatism in that State, less than 30 per cent were directly under medical care; the remaining 70 per cent were either attempting to treat themselves or were receiving no treatment at all. Many of these people had lost confidence in the curative value of the treatment they had previously employed, others were unable to finance the cost of care.

Unfortunately, the incidence of arthritis among the poor is about 50 per cent higher than among the well-to-do. Many poor people who might realize the dangers involved in delaying adequate treatment are unable to pay for it. We thus come to the last and probably the most important reason for the present unsatisfactory status of the arthritis problem, *the lack of facilities.*

In an effort to determine the nature and extent of existing facilities throughout the United States, the writer undertook to make as thorough a survey as possible of physicians, hospitals, clinics and other reliable sources of information. This survey disclosed the following:

Unlike the situation with respect to certain other chronic diseases, par-

ticularly tuberculosis, the arthritis victim lacking the means to finance his treatment is almost entirely dependent on the personal interest, resources and facilities of private hospitals and physicians.

At present little if any provision is made in the average general hospital program for the chronic arthritis patient. A general hospital may have facilities for free emergency cases, but no voluntary and hardly any public hospital can treat or help an arthritis victim free of charge long enough to do him any appreciable good. Furthermore, a general hospital and its staff often look upon these patients as nuisances; little interest is shown in them compared to that taken in patients suffering from acute diseases of a more spectacular nature offering prospects of rapid cure. There is a feeling of futility in attempting to help the victim of chronic arthritis.

Throughout the entire United States there is no hospital or institution devoted exclusively to the treatment of arthritis. Most private hospitals in the larger cities do maintain some degree of facilities for arthritis patients. In Boston, New York, Philadelphia, Chicago, Rochester, Minn., Ann Arbor, Michigan, St. Louis, Hot Springs, Ark., Tucson and San Francisco, for example, there are outstanding and well-organized clinics for arthritis. However, very few of such hospitals or clinics can treat or hospitalize their patients free of charge. There are also a number of well-known and splendidly equipped spas in the United States to which the well-to-do can repair for treatment and cures. At Saratoga Springs, N. Y., the State provides treatment facilities comparable to the best in the world and, although these facilities are available to needy patients of the State free of charge upon their physicians' certification of eligibility, no hospitalization is provided and such patients therefore must bear the not inconsiderable expense of room and board themselves. Furthermore, while it is true that many state and county hospitals endeavor to make some provision for poor patients suffering from rheumatic diseases, whatever facilities are available often are contingent upon such admittance conditions and requirements that the number of dependent chronic arthritics actually hospitalized or adequately cared for is negligible.

Compared to the staggering economic costs of arthritis, practically no funds or facilities of any importance are available from outside sources to help the medical profession attack the disease. Except for the specific grants listed below, all hospitals, clinics and spas in the United States at present caring for arthritis victims operate entirely at their own expense:

The Robert Breck Brigham Hospital of Boston has 25 free beds available.

The Massachusetts General Hospital of Boston has 25 beds supplied by the Commonwealth of Massachusetts and a donation of $30,000 per annum from a private source which is used for research.

The Leo N. Levi Memorial Hospital of Hot Springs, Arkansas, has 75 free beds, together with a complete clinical and research department.

The Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital in New York City receives an income of approximately $15,000 per year which is devoted almost exclusively to research. No free beds are provided.

The Research Hospital for Chronic Diseases, Department of Hospitals, New York City, has 10 or 12 beds available for patients suffering from rheumatoid arthritis.

Bellevue Hospital, New York City, has from ten to thirty beds set apart and constantly occupied by patients suffering from rheumatic diseases.

The Cornell Medical Center of New York City receives an annual endowment of $25,000 for research.

The University of Michigan has the use of the income from $1,000,000 per annum for research, but at present no free beds are available.

Thus, as far as could be determined, there are not more than 200 free beds specifically available today for arthritis victims unable to pay, and not more than $200,000 is provided from outside or private sources to help finance the research so vitally important successfully to combat the disease. Compared to the figures of more than 100,000 free beds and over $100,000,000 available for research in tuberculosis and the care of its victims, the vast disproportion appears out of all reason.

As a result, up to the present time many physicians who might be interested in learning more about the problem of arthritis are handicapped by the almost complete lack of facilities for postgraduate study and research in chronic rheumatic diseases. It is significant that of a total number of 77 recognized medical colleges in the United States, as far as the writer could determine there are but six (Harvard, Cornell, College of Physicians and Surgeons, New York University, University of Michigan and the University of Pennsylvania) which offer opportunities or facilities for the specialized study of these diseases. The University of Pennsylvania is the only one of these colleges that offers an opportunity for postgraduate study in the treatment of arthritis. Its course, which is under the direction of Dr. Ralph Pemberton and his associates, is well organized, has abundant material and affords excellent training to any doctor interested in improving his knowledge regarding the most efficient methods of treating the various types of arthritis. This course probably represents the first organized teaching on the subject available in the country.

At first glance the results of the writer's survey would seem to be far too discouraging to warrant the hope that any material improvement of existing conditions might be possible. However, if it is recognized that the problem is far too vast for the medical profession to handle alone and that it is a sociologic one requiring the combined interest, efforts and assistance of society at large, the handicaps involved are certainly no greater than those confronting the other chronic diseases in the past which have been successfully and even spectacularly overcome.

The marvelous progress made against tuberculosis during the last 35 years is an outstanding example of what can be done. Up to 1904, that disease was very definitely on the offensive and no united defense, voluntary or official, had been made against it. Of course, the spectacular starting point of its crusade was Dr. Trudeau's courageous personal campaign against

the disease. This accomplished much to arouse interest and led to the establishment of the first small sanatorium at Saranac, N. Y. However, quickly following upon the noted achievements of Dr. Trudeau and others, a group of 400 far-sighted physicians and laymen organized the National Tuberculosis Association, which, although handicapped by a general lack of interest and funds, nevertheless took prompt aggressive action. Faced with the added incentive of having the next meeting of the International Congress for the Study and Control of Tuberculosis in New York in 1905, they successfully appealed to the Russell Sage Foundation. It was largely the financial assistance received from that organization during the following ten years that enabled the Tuberculosis Association to organize successfully its campaign for a national crusade which has resulted in the widespread interest and coöperation clearly indicated by the enormous resources and splendid facilities for research and treatment available today throughout the entire country.

The nature of the arthritis problem in this country today presents a close parallel to the early conditions confronting tuberculosis. Brilliant pioneers have been active since as early as 1904. For instance, Dr. Goldthwaite and his associates, Drs. Osgood and Painter of Boston, made valuable contributions on the importance of rest and posture in the prevention of deformities associated with arthritis. Drs. Billings and J. Miller of Chicago made equally valuable contributions, the former on the importance of focal infection and the latter on the relative value of non-specific vaccines; Dr. Pemberton of Philadelphia, an outstanding leader in arousing greater interest in arthritis, emphasized the importance of restricting the diet and the possible rôle of carbohydrates. Drs. Richardson and Nichols published an important article on the pathology of the joints.

Furthermore, largely influenced by the Mayo Foundation, definite efforts to develop a widespread awakening of interest among the members of the profession have been under way for the past ten years. In this connection, a brief review of the history of the problem in Europe as it ties up with activity to date in this country might be of interest. Parenthetically, although the level of medical effort in combating arthritis is probably higher in the United States than it is anywhere else in the world, authorities both here and abroad are unanimously agreed that we thus far rank far behind in a proper appreciation of its sociologic and economic importance. Such lack of interest would seem to be substantiated by a survey made of our leading insurance companies to determine the extent of the admitted heavy demands made upon them for disability payments arising from arthritis. Practically without exception, no serious attempts had been made by these companies to break down their statistics and as a result it was impossible to obtain reliable information regarding incidence and economic costs from those presumably well-informed sources.

In England after the World War, the insurance companies were largely instrumental in directing attention to the alarming incidence and cost of

rheumatic diseases there. A report prepared at the instigation of the British Ministry of Health in 1924 by Dr. J. Alison Glover fully confirmed their astounding incidence and pressure on industrial workers as well as the economic losses involved. General interest was aroused which eventually resulted in the organization of an International League for the Study and Control of Rheumatic Diseases (Ligue Internationale contre le Rheumatisme). Most European countries quickly became acutely conscious of the economic importance of the problem and many national societies are today strongly attacking it with, in many cases, important financial assistance from outside sources. Many of the European societies publish journals devoted exclusively to activities in rheumatic diseases at home and abroad, thus maintaining general interest.

Recognizing the desirability of a mutual exchange of ideas with the United States, Dr. Van Breeman of Holland, while he was president of the International League in 1928, asked Dr. Louis B. Wilson, Director of the Mayo Foundation, to suggest names for an American Committee. In collaboration with two Mayo colleagues, Drs. Henderson and Hench, and Dr. Osgood of Boston, Dr. Wilson selected a tentative group of men, all of whom, because of the high character of their work, university affiliations and professional writings, had indicated a sufficiently deep interest in the arthritis problem to constitute a representative American body. This group became the American Committee for the Control of Rheumatism and its first meeting was held early in 1928 with Dr. Pemberton as Chairman and Dr. Henderson as Secretary. The other members of this first committee were Drs. Osgood, J. O'Reilly and Zinsser of Boston, L. Barker of Baltimore, C. C. Bass of New Orleans, R. Cecil of New York, R. Haden of Cleveland, Joseph I. Miller of Chicago, and Rea Smith of Los Angeles.

The International League for the Study and Control of Rheumatic Diseases (Ligue Internationale contre le Rheumatisme) is to hold its next annual conference in this country in 1940. It is hoped that by that time sufficient progress will have been made in the development of a general arthritis campaign so that as creditable a showing will be made at that meeting as was made by the National Tuberculosis Association at the first International Congress on Tuberculosis held here in 1905.

During the years 1930, 1931 and 1932, the American Committee met on the first day of the annual meeting of the American Medical Association. Physicians of high caliber, known to be interested in arthritis, were invited to attend these meetings. Attractive programs were offered which consisted in the presentation and discussion of a necessarily limited number of papers and the sponsoring of exhibits on arthritis simultaneously with the exhibits presented by the American Medical Association on other subjects. At a later date, all the papers read at these meetings were published in the form of a Symposium on Arthritis.

In 1933, through the efforts of the Committee, the American Rheumatism Association was formed for the specific purpose of promulgating and

exchanging ideas among professionally qualified students of rheumatic diseases, encouraging intensive study of them, and spreading sound doctrines of prevention and treatment.

This Association has proceeded cautiously in its expansion, adhering to rigid qualifications for membership in order to maintain the highest possible medical standards. As a consequence, its present membership is not large, although from an original number of 26, it now has slightly over 200 members.

Every year since its formation the Association has appointed a Reviewing Committee comprised of members representative of a cross-section of the country, which unselfishly devotes a great amount of time and effort to the review of more than 600 articles on arthritis which have appeared during the year in English and American literature. This year's Reviewing Committee is comprised of Dr. Hench of Rochester, Minn., W. Bauer of Boston, R. Dawson of New York, Holbrook of Tucson, J. A. Key of St. Louis, and Francis G. Hall of Boston. Worthwhile abstracts of all articles reviewed and comment thereon appear annually in the ANNALS OF INTERNAL MEDICINE.

As further indication of the extent of activity, it should be mentioned that both the American Committee for the Control of Rheumatism and the American Rheumatism Association have the important and most cordial support of the American Medical Association, which has opened its programs and Journal to an increasing number of reports on arthritis, thus bringing important developments and activity in that field to the attention of its more than 150,000 subscribers.

A few papers of special interest to laymen are published annually in *Hygeia,* and the American Rheumatism Association has created associate memberships for interested laymen, social workers, insurance executives and members of professions allied to medicine. All these associate members receive bulletins summarizing information of current interest in arthritis.

From the foregoing outline of activity in this country, it is obvious that interest on the part of the medical profession has not been exactly dormant with regard to the arthritis problem. The framework for the start of a campaign has been erected. We must now proceed to build upon this framework and develop a permanent structure. This development should follow four main lines, i.e., (1) publicity; (2) education of general practitioner; (3) improvement of existing facilities and (4) research.

As a first step, the incidence, personal dangers and devastating economic consequences of arthritis should be dramatized and so forcefully emphasized to the public that the extreme need for increased interest and action will be clear to everyone. To do this most effectively, a small publicity department, preferably as an adjunct to the existing American Rheumatism Association, should be established without delay. This department should avail itself of such facilities as the radio, press and popular magazines to help drive home its objectives.

Along with such publicity, the American Rheumatism Association should sponsor and encourage further postgraduate education of the general practitioner by means of lectures, exhibits, bulletins, journals and actual contact with recognized, well-organized and efficiently operated arthritis clinics. Increased efforts should be made to interest properly qualified physicians to join the Association.

Every large general hospital which at present has clinical facilities for the treatment of arthritis should be impressed with the need of having such facilities conform to the Minimal Standard Requirements for Arthritis Clinics established by the American Rheumatism Association. A feature of these Requirements which would be of inestimable value would be the provision of a certain limited number of free beds in each hospital devoted exclusively to the detailed study and treatment of certain arthritis cases by the staff of the Arthritis Clinic connected with the hospital. Later, the development and establishment of new clinics and facilities conforming to the Minimal Standard Requirements should be considered. As such present and future clinics are duly recognized, arrangements should be made to have them listed in the Hospital Number of the *Journal of the American Medical Association* under the caption " Annual Presentation of Hospital Data."

Simultaneously with such efforts to improve existing facilities, the cooperation and financial assistance of private patients and philanthropists must be obtained in order to carry on the all-important research as to the causes of arthritis and the study of present and new methods of treatment.

In conclusion, the writer must express his conviction that in his opinion, there is nothing more satisfying to the physician than the gratitude of a rehabilitated arthritis patient, and that there is no finer or more worthwhile medical task than the control of a disease which exacts such an astounding toll from the community. However, from past experience in other crusades against chronic disease, it is known that the medical profession, no matter how outstanding its men, brilliant their research and high their ideals, can accomplish little by itself. All available resources must be combined as quickly and effectively as possible to combat the continued ravages of arthritis and assure the rehabilitation of an ever-increasing number of its victims.

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OIL ASPIRATION PNEUMONIA AND PNEUMOLIPOIDOSIS *

By PHILIP G. C. BISHOP, M.D., *New York, N. Y.*

THE classical case reports and animal experiments of Laughlen [65] in 1925 dealing with a " specific " lung reaction to aspirated oil and lipoid substances have awakened considerable interest in clinical, pathological and experimental aspects of this subject.

It is hoped that a summary of the cases found in the literature to date, together with a report of new cases, will upon analysis indicate certain trends that may be useful (1) in guiding the clinician to earlier recognition of this rare disease; (2) as a stimulus to further studies and correlation of the facts found; (3) in offering suggestions in prevention and treatment.

TERMINOLOGY

The term lipoid pneumonia is probably the one that is most frequently employed at present. Inasmuch as most of the cases reported clinically or at autopsy show some degree of pneumonia, it is perhaps reasonable that this term should be included in naming this disease. Again, inasmuch as the etiological agent is either an oil (mineral oil) or a lipoid (vegetable or animal) either the term " oil " or " lipoid " should logically be included. Third, the disease is usually produced under conditions favoring aspiration of the offending agent. Therefore, the term " oil aspiration pneumonia " (Ikeda [53, 54]) seems suitable when the offending agent is a form of mineral oil. However, when the offending agent is a true lipoid, the author prefers the term " pneumolipoidosis "—a term which denotes the organ involved, the causative agent, and the accumulation or increase of lipoids in the pulmonary parenchyma—free or intracellularly. This latter term also becomes available for the few cases in which there is no pneumonia due to bacterial infection, and where the lipoidosis may be of endogenous nature, as suggested by some authors.[19, 51, 85]

" Oil aspiration pneumonia " and " pneumolipoidosis," therefore, broadly cover the various phases of this clinico-pathological picture.

INCIDENCE

An exhaustive search of the literature to date reveals 136 cases (tables 1 and 2) either *mentioned* or fully reported, the majority of which were diagnosed at autopsy. These reports were made in a period of 12 years from 1925 to 1938. However, some of the pathological material from

* Read before the Medical Section of the New York Academy of Medicine, May 17, 1938. Received for publication December 19, 1938.

TABLE I

Authors and Oil Aspiration Pneumonia Cases as Reported

Year	Author	Number of cases	Year	Author	Number of cases
1925	Laughlen, G. F.	5	1935	Karelitz, S.; Denzer, B. S.	1
1926	Thomas, W. S.; Jewett, C. H.	1	1935	Langdon, J.	1
1927	Pinkerton, H.	6	1935	Normand, P.	1
1930	Valobra, N.	1	1936	Ball, F. E.	1
1931	Brüning, H.	1	1936	Baumgartner, L.; Angevine, D. M.	3
1932	Pierson, J. W.	4	1936	Davis, K. S. (one identical with that of Houck)	3
1932	Pollak, B. S.; Potter, B. P.	1	1936	Houck, G. H.	1
1933	Bodmer, H.; Kallos, P.	1	1936	Klinck, G. H., Jr.	1
1933	Fischer-Wasels, B.	1	1936	Reineke, H. G.; Whiteleather, J. E.	4
1933	Meursing, F.	2	1936	Ritchie, G.	12
1934	Ellinger, E.	3	1936	Tchertkoff, I. G.; Ornstein, G. G.	10
1934	Goodwin, T. C.	25	1937	Brenner, F.; Urban, F. F.	2
1934	Grayzel, D. M.; Du Mortier, J. J.	3	1937	Fetterman, G. H.	2
1934	Hayes, J. N.; Gardner, L. U.	3	1937	Ikeda, K.	5
1934	Rabinovitch, J.; Lederer, M.	6	1938	Paterson, J. L. H.	8
1935	Boyd, W.	1	1938	Bishop, P. G. C.	3
1935	Cannon, P. K.	1			
1935	Garrison, H. F.	1			
1935	Graef, I. (read)	6			
1935	Ikeda, K.	7			

Total cases = 136

TABLE II

Oil Aspiration Pneumonia

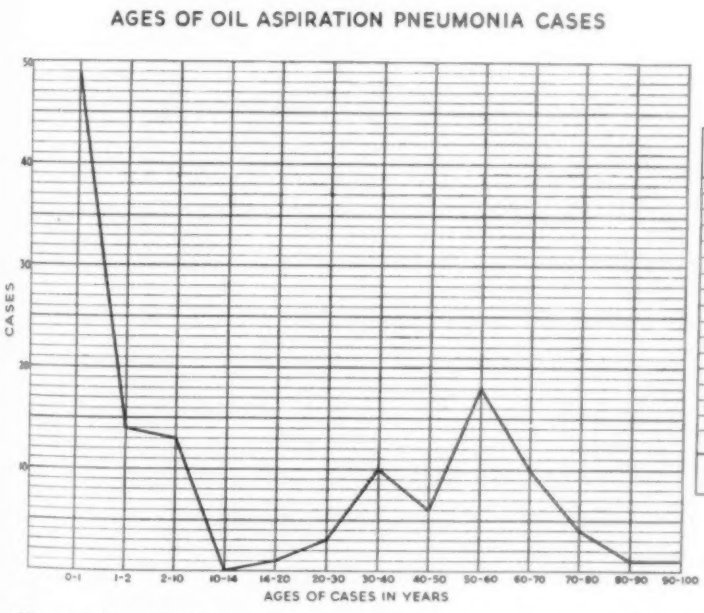
Total number of cases of oil aspiration pneumonia		136
A. Living cases	20	
I. Cases diagnosed as oil aspiration pneumonia in life	23	
1. Cases diagnosed and living	20	
2. Cases dead but diagnosed in life	3 (Baumgartner and Angevine 2, Davis 1)	
B. Patients who died	116	
II. Cases autopsied	112	
3. Cases diagnosed in life and autopsied	2 (Baumgartner and Angevine)	
4. Material obtained by bronchoscopy (post mortem)	1 (Reineke and Whiteleather)	
III. Pathological examination not specified	2 (Pierson)	
IV. Cases without autopsy	2 (Reineke and Whiteleather 1, Davis 1)	

which the diagnoses were made dates back at least to 1902 (Normand's case,[71] also reviewed by Comby[19]). When this present total of cases is compared to the enormous quantity of lipoid agent used medicinally, as dispensed by hospitals, institutions, drug stores, and private physicians throughout the country and the world, the incidence of the disease entity becomes numerically insignificant. Rarity of occurrence is further brought out by the fact that Laughlen[65] added a fifth case to his series of four only after a search through 300 autopsy cases in the year preceding his report. Pinkerton[76] found six cases in a search through 290 consecutive autopsies, and Ikeda reports a case of "chronic oil aspiration pneumonia" in an adult woman, the only one found in several thousand necropsies in the past several years. On the other hand, a number of cases have remained undiagnosed

in life and at autopsy, and some diagnosed cases have not been reported. Therefore, it is well to be conservative in comments on statistics until a larger series of bona fide cases has been collected.

Diagnosis

As yet the diagnosis during life is not dependent upon *one* or *several distinctive diagnostic* features, but a strongly presumptive diagnosis is arrived at by elimination in differential diagnoses. This is even true perhaps in the case of the so-called typical chest roentgen-ray. Barring certain variations the diagnostic features are by and large similar in children and adults. The onset is insidious. The disease is rarely uncomplicated. The patient is first seen due to another disease or complication. The majority of the cases occur in the period of infancy up to two years of age, with a second rise in the age group of beginning debility, the fifth and the sixth decades (figure 1).



	Age	Number at various Ages	Living	Dead	Confirmed at Autopsy
	INFANT	2	0	2	2
	0-12 MOS.	47	3	44	43
63	12-24 "	14	0	14	14
	2-10 YRS	13	1	12	12
13	10-14 "	0	0	0	0
	14-20 "	1	0	1	1
	20-30 "	3	3	0	0
14	30-40 "	10	5	5	5
	40-50 "	6	4	2	2
	50-60 "	18	3	15	14
34	60-70 "	10	0	10	10
	70-80 "	4	0	4	4
	80-90 "	1	0	1	1
	90-100 "	1	0	1	1
8	ADULT	2	0	2	2
	NOT GIVEN	4	1	3	1
	TOTAL	136	20	116	112

Sex: male, 80, female, 43, not given, 13.
Color: colored, 14, white or not given, 122.

Fig. 1. Showing the preponderance of cases occurring in the first year and the sixth decade.

History

The special facts to be obtained from the routine systematic history are, of course, detailed information on the use of an oily or lipoid agent. Not only should the quality of the agent be known (table 4) but also the amount, the frequency, and the duration of its use. Furthermore, the mode of administration should be inquired into (figure 2), whether by mouth, pharynx, nose or by trachea; and the position of the patient during administration

should be determined. Inquiries about feeding difficulties or conditions favoring aspiration of food should be made in order to rule out the lipoids of food as a possible causative agent. If the additional trouble is taken to make such inquiries in all cases that present atypical and prolonged pulmonary disorder, an early clue to a possible instance of this disease may be obtained. When the volunteered symptoms have been given, further specific inquiry into symptoms and conditions that may favor aspiration should be made. Such inquiry may reveal reduction or abolition of the swallowing or cough reflex.

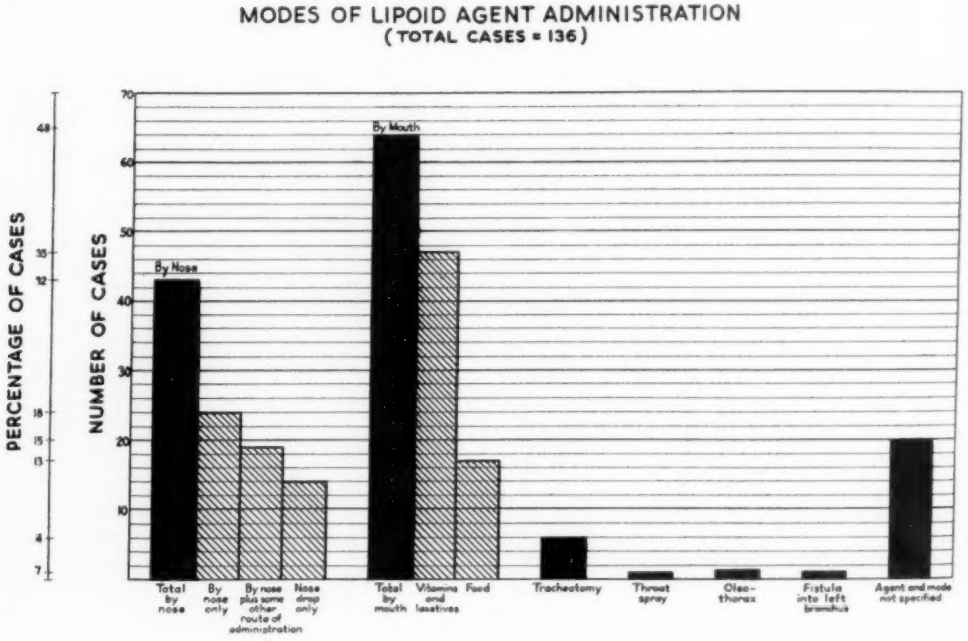


FIG. 2.

A history of cough, choking, gagging, regurgitation, vomiting and hiccoughing is frequently given. Such conditions are factors in enhancing aspiration (table 3).

Immobility and recumbent position, especially if prolonged, are noteworthy, inasmuch as insidious aspiration is at least more favored in the flat position than when the patient is erect or ambulatory.

PHYSICAL EXAMINATION

There are no specific diagnostic signs. As Goodwin [38] says, such signs as may be found are difficult to evaluate inasmuch as the condition is usually accompanied by some other and more severe illness or complication.

The nutritional and developmental status of the patient is usually impaired. Children, as observed by Goodwin,[38] are frequently stunted in

TABLE III

Symptoms or Conditions Which May Favor Aspiration

	Conditions or symptoms found. Number of cases	Conditions or symptoms found during period of lipoid agent administration. Number of cases
Cough	51	40
Vomiting	42	31
* Impaired general condition	39	39
Difficult feeding	34	22
On back in bed	17	14
Dysphagia	17	13
Convulsions	15	7
Coma	11	6
Gagging	10	2
Choking	8	6
Stupor	6	3
Paralysis	4	4
Subdued reflexes	4	3
Never sat alone	2	2
Plaster cast—unable to hold head, sit alone	2	2
Twitchings	1	1

* Including: "Failure to gain, underweight, underdevelopment, nutritional disturbance, malnutrition, emaciation, marasmus, inanition, weakness."

growth, and wasting and emaciation are frequently recorded. In the more severely ill patients various nervous disorders such as irritability, convulsions, listlessness, stupor, and coma have been observed. Rapid respirations are a frequent finding, in children usually without dyspnea, and in adults with occasional cyanosis. Clubbing of the fingers has been found in several cases but is more likely accompanying chronic pulmonary diseases.

Fever is present but its degree and course are not typical. The pulse is as variable as the fever and may be disproportionate to it. Upper respiratory infection is frequently present. Examination of the chest reveals a variety of signs. There is always a varying degree of impaired resonance, especially over the lower inner chest areas of one or both sides, and usually there are bronchial or parenchymal râles. As the condition progresses these signs will persist with relatively minor variations. Marginal or over-lying emphysematous breath sounds may be heard. These findings are frequently confused by the signs of other complicating lung disease. Occasionally findings associated with right heart failure secondary to extensive pulmonary fibrosis may be present. Enlargement of the spleen and lymph glands is found not infrequently without apparent clinical causal relationship (figure 3).

ROENTGEN-RAY

The most important diagnostic aid to date is the chest roentgen-ray appearance (figures 6, 7, and 8). This is brought out by several authors,[84] but in particular by Goodwin.[38] What may be considered a typical roentgen-ray is one that shows a shadowing found in the peri-hilar region, bilaterally or unilaterally, which reaches towards the peripheral lung fields depending

TABLE IV

Lipoid Agent and Identification of Oils

			Agent	Identification	Looked For But Not Found
Mineral oil	Mineral oil (paraffin, liquid petrolatum, albolene, nujol, etc.)		59	20	
	Mineral oil in combination		24	(a) 3	1
	Not specified, but probably mineral oil		3		
	Not specified, but probably mineral oil in combination		3		
	Total: Mineral oil used with or without combination	89			
Food fats	Cream		1		
	Milk		11	1	
	Egg yolk		1	1	
	"Oil and fat"		1		
	Food		2	1 (Butter fat)	
	Probably food		7		
	Total: Food fats	23			
	Cod liver oil		30	(b) 8	1
Vitamins	Haliver oil		3	1	
	Viosterol		4	2	
	Total: Vitamins	37			
Non-mineral oils	Castor oil		2		
	Olive oil with ephedrine inhalant		1		
	Glycerine with vaseline		1		
	Gomenol		1		
Non-lipoids given with lipoid agents	Argyrol		1		
	Neosilvol		1		
	Silver nitrate		1		
	Denied by history		6		1
	Lipoid agent not stated		16	2	
				39	
Medicated lipoid agents	Ephedrine jelly				
	Paraffin with menthol				
	Liquid petrolatum with menthol				
	Liquid petrolatum with thymol and menthol				1

(a) Liq. petro.
Paraffin oil
Mineral oil

(b) Plus butter fat 1
Plus liq. petro. 2
Plus mineral oil 1

PERCENTAGE OF DEAD CASES

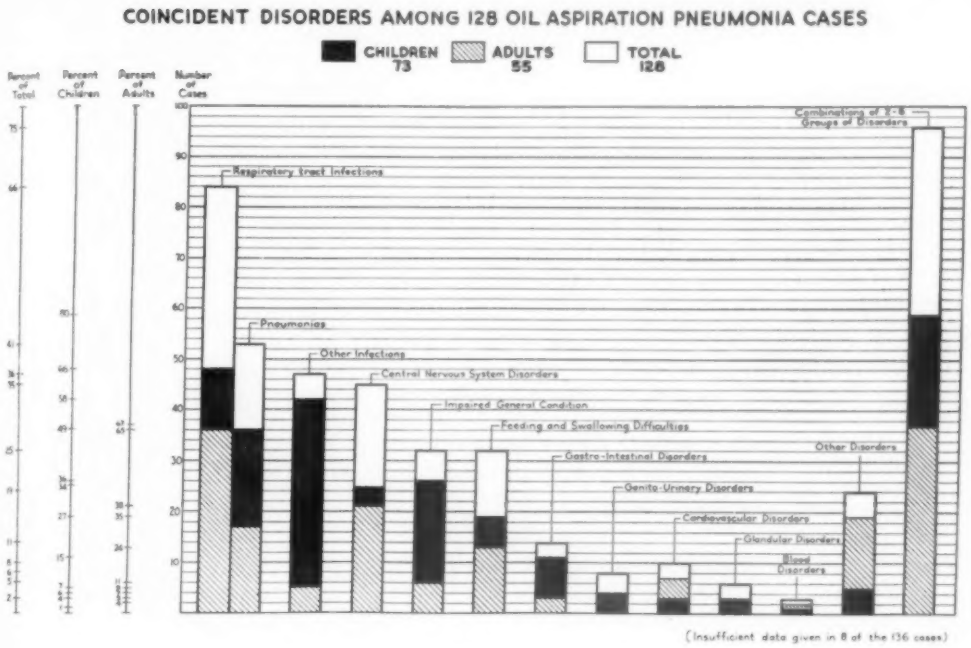


FIG. 3.

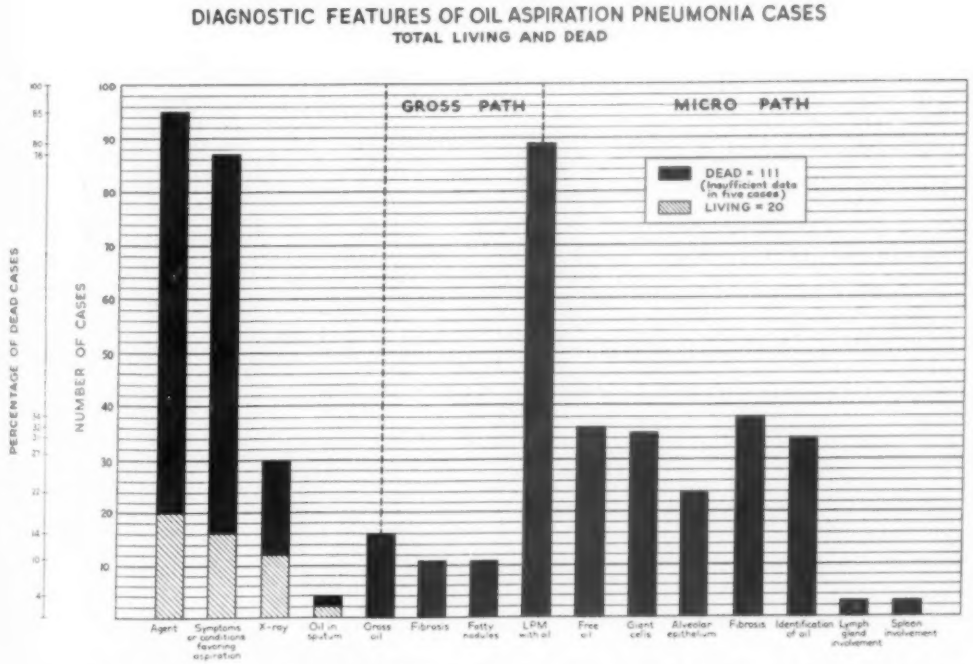


FIG. 4. Note that by far the majority of cases have been diagnosed on three factors: Agent, symptoms favoring aspiration, and the presence of large phagocytic monocytes containing oil droplets found on microscopic section of the lung at autopsy.

upon the duration and extent of the disease. The opacity may vary in quality from a more or less central consolidation almost of the quality of calcification, to a fine haze which towards the periphery is barely denser than normal lung shadows. There is, therefore, an outline of involvement usually without sharp demarcation. Pneumonic consolidation is the frequent report after inspection of such a chest film. There is a distinct foreign body type of distribution with the right side more affected than the left, the lower lung fields more than the upper, and the posterior areas more than the anterior. On close inspection these shadows may suggest the fine fibrosis and peri-bronchial thickening always present in this disease (figure 8).

Other conditions to be differentiated by roentgen-ray are Ayerza's disease, bronchiolitis fibrosa obliterans,[85] pneumoconiosis,[27] syphilis of the lungs,[31] and some cases of protracted disseminated hematogenous pulmonary tuberculosis. The oil tumors sometimes found in gross pathology may occa-

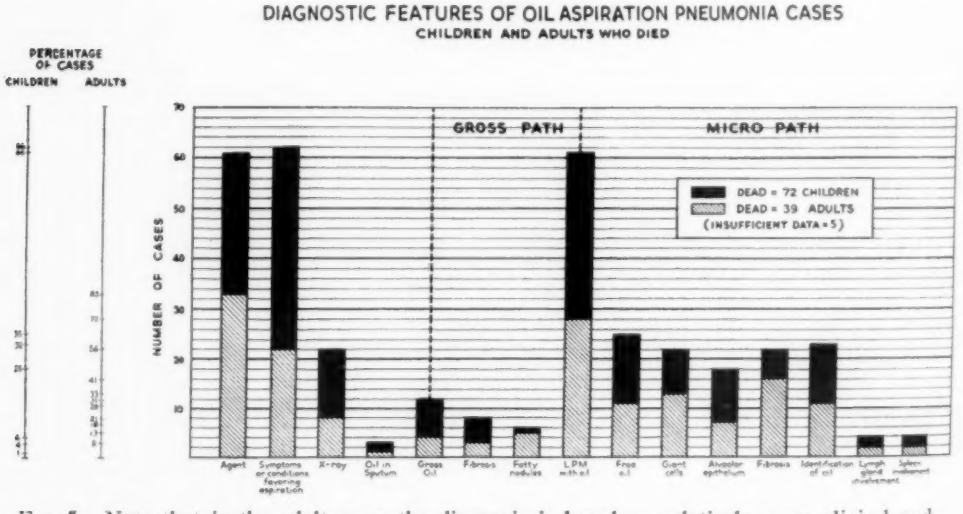


FIG. 5. Note that in the adult cases the diagnosis is based on relatively more clinical and pathological factors than in the cases of children.

sionally be identified in the roentgen-ray on retrospection but their shadows are difficult to interpret ante mortem. In the present series, the roentgen-ray picture is often complicated by the shadows produced by other pulmonary disorders.

The final important feature in the roentgen-ray diagnosis is the relative lack of change [38] in serial roentgen-rays, with only gradual and minor regression being observable over a period of months and years (figures 6 and 7).

LABORATORY AND OTHER TESTS

In the present series of cases almost every laboratory test has been made. They are incidental and non-specific. Positive findings are related to the associated disorders. The blood lipoids do not reveal any clue to the existence of this condition.

The sputum examination (centrifuged, blocked, sectioned and stained) for the presence of free oil droplets or for phagocytic cells enclosing fat droplets is of interest, should be done, but is not diagnostic by itself. Several authors [47, 51] have reported positive findings in this examination (figures 4 and 5). However, Quensel [80] in numerous normal lungs and in sputa of normal persons reports that he frequently found fat substances, free and in the alveolar epithelial cells.

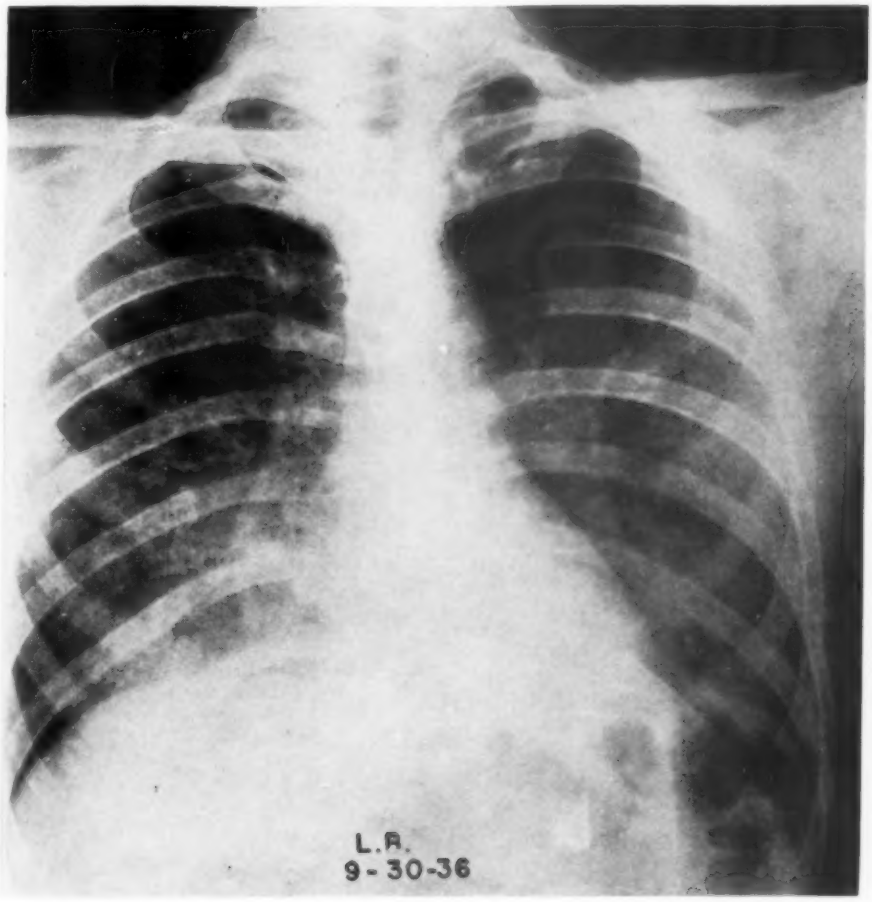


FIG. 6. (Case 1.) Chest roentgen-ray upon first admission reported as showing lack of change over films taken elsewhere in May, July and September of the same year.

In one of the cases herewith reported, these findings were at first positive, but later even bronchoscopic suction failed to yield material for examination, which may indicate a change from free drainage of lipoid substances earlier in the disease to the later stage where the lipoids are deposited, entrapped and fixed in the lung.

Although mention has been made of possible lessened vital capacity in this condition, no record of actual estimation has been found in the entire reviewed literature. In one of my cases in which the vital capacity estimations were made, the results were normal and approximately the same during an interval of six months.

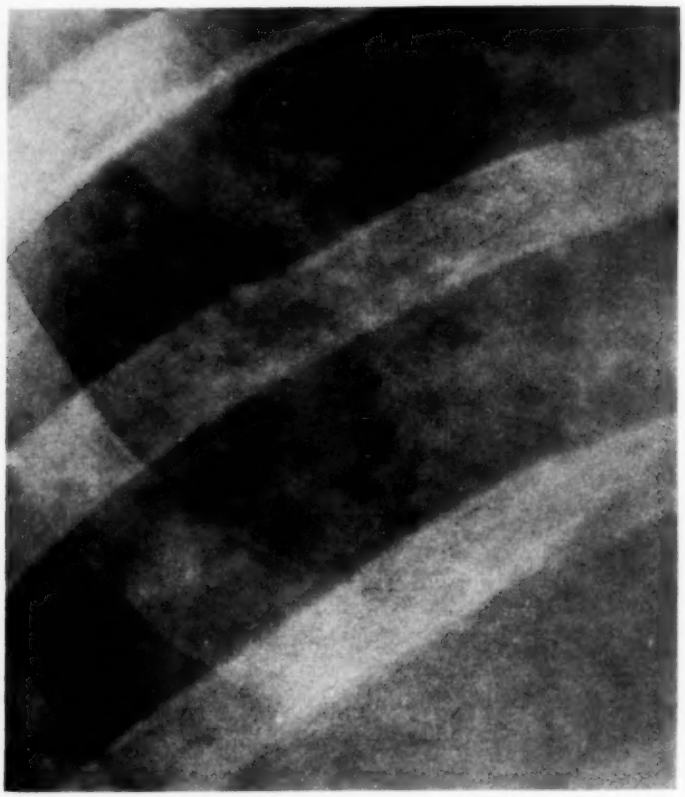


FIG. 7. (Case 1.) Greater detail of June 1937 chest roentgen-ray at margin of involvement of the right lung showing areas of condensation and rarefaction probably corresponding to areas of oil or lipoid infiltration with normal lung tissue intervening. Note the fine fibrosis.

CHEMISTRY

Identification of the offending agent in the lung specimen has frequently been made in this series of cases but not, however, as frequently as the opportunities would warrant. Even more frequently a non-qualified fatty substance has been identified by means of the usual fat stains. Several authors (as Pinkerton,[76] Ikeda,[53] and Fischer-Wasels [31]) have gone into detailed chemical study of the pathological material by the combination of stains, Ciaccio's method, solubility, iodine number, fatty acid content, and Nicol prisms (figures 4 and 5; table 4).

Quantitative estimations and differentiations of the lung fats found have also been made, and compared with the normal fat content of normal and diseased lung, show results in quantity and quality unlike that in other known lung disease.

A detailed discussion of the fat chemistry is not the scope of this paper but it may be emphasized that it is by means of chemical analysis that final

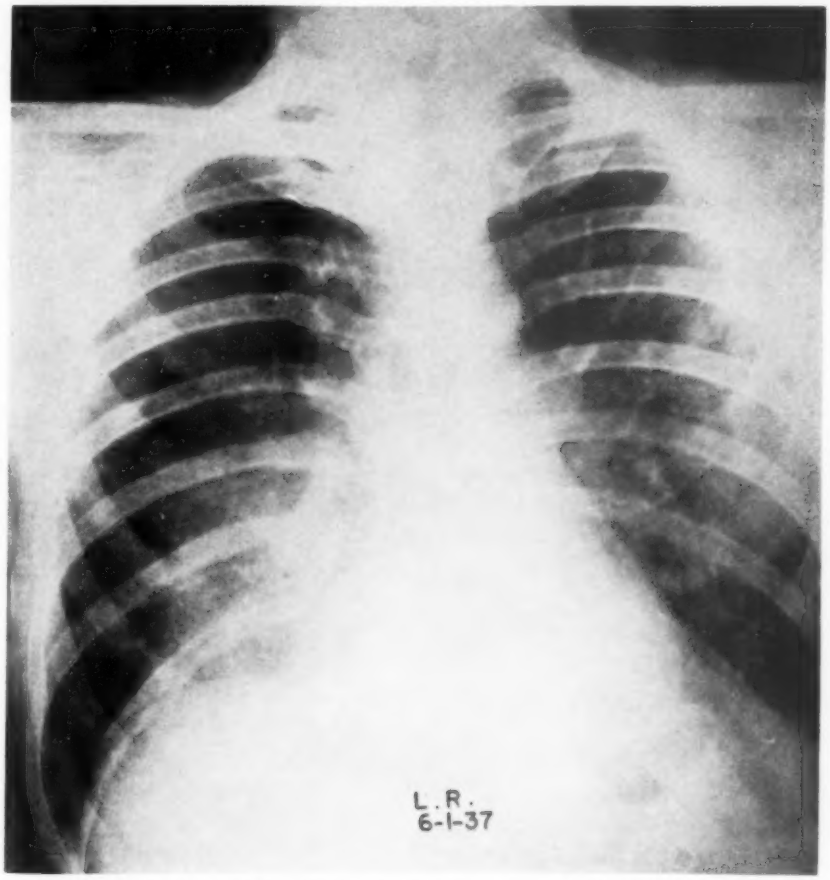


FIG. 8. (Case 1.) Chest roentgen-ray upon second admission eight months later still showing a lack of change and typical in appearance of oil aspiration pneumonia or pneumolipoidosis.

diagnostic proof is obtained and the suggestion presents itself that further chemical studies will confirm or refute the differentiation here suggested between oil aspiration pneumonia and pneumolipoidosis, exogenous and endogenous.

PATHOLOGY

The diagnostic findings are limited primarily to those found in the lungs and secondarily to those found in the lymphatic system, and here, mainly in the regional lymph nodes and occasionally in the spleen. If one considers

exogenous and endogenous varieties and the possibility of a faulty fat metabolism or lipoid dyscrasia, then the examination of all organs and tissues available at post mortem should be made and fully reported in the hope that findings may be correlated which will confirm or refute the existence of two clinical varieties and of a metabolic disturbance (Houck[51]).

The gross appearance of the lung usually presents a mixed pathological picture. The specifically involved portions appear as yellow mottled areas over the pleura. These areas may be very small and discrete or may involve one or more entire lobes of the lung, depending upon the duration and extent of the disease. On palpation these areas are firm and rubbery. On cut section of the lung gross oil is occasionally found and sometimes, as noted by several authors, has a characteristic fish odor[3] when the offending agent was fish liver oil. At other times gross oil is noted when the cut surface is scraped with the knife. If this is the case, scrapings may be placed on a slide and stained for fat, yielding a quick and important diagnostic finding. I should like to recommend this simple test (as done by Thomas and Jewett[101]) as a routine postmortem procedure.

On cut surface, the involved areas have a white, yellow, or orange-yellow appearance unlike the usual picture of pneumonia. These areas may be discrete or may gradually merge into the adjacent lung tissue. Calcification[38] has occasionally been noted, as has necrosis[77] and hemorrhage. Almost invariably, however, this pathological picture is obscured by pneumonia, atelectasis, or emphysema. It is rarely uncomplicated at autopsy.

The microscopic picture varies according to the type of offending agent involved and it is well to refer to Pinkerton's article[77] for a detailed description of the varieties.

The progressive lesion produced may be described briefly as follows: Free droplets of fat or oil are found in the alveolar spaces. Large mononuclear phagocytes appear which take up this substance. The droplets and the oil- or fat-laden phagocytes permeate the septal and interstitial tissues and finally enter the lymphatics. They may thus reach the regional lymph nodes[51] and eventually through the larger lymph channels or through alveolar capillaries they may reach the spleen through the general circulation. They may also fill the atrial spaces and extend into the bronchioles and bronchi. Concomitantly, there is a change in the alveolar epithelium which is transformed into a low cuboidal type. In the septa and interstitial tissue, progressive fibrosis takes place (figures 11 and 12). Up to this stage, the picture may well represent a pneumolipoidosis of endogenous or early exogenous nature. By this time the phagocytic activity has progressed to the state where coalescence of the individual cells has taken place to produce giant cells. The fibrosis is one of the outstanding pathological features of this disease and may progress to the extent of forming gross bands traversing the pulmonary field or even shrinking an entire lobe down to a fibrous residue (Fischer-Wasels[31] and Bodmer and Kallós[8]). Round cell infiltration is found here and there in the microscopic section, sometimes to the extent of forming

new lymph follicles, particularly along the lymph channels in the walls of alveolar capillaries and of the bronchioles, as demonstrated by Pinkerton.[76]

When the regional lymph nodes are invaded, they may be enlarged with very little fibrosis and small tubercle-like nodules may be visible but the lipoid invasion can at best only be suspected on gross pathologic examination. Microscopically, a scattering of oil droplets is found in the periphery of the follicle and in the sinuses. Scattered through the spaces of the node may be seen macrophages with carbon and oil globules (Thomas and Jewett [101, 77]). When the spleen is involved,[76] a similar picture is found.

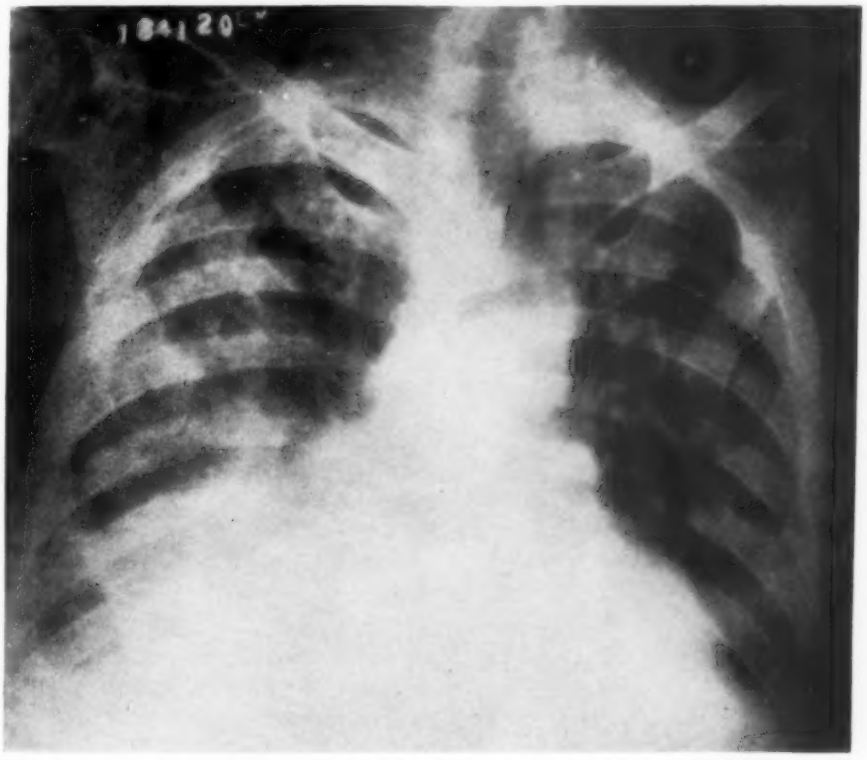


FIG. 9. (Case 2.) Bedside chest roentgen-ray taken 13 days before death showing what was interpreted as right lower lung pneumonia with pyopneumothorax and chronic thickened parietal pleura from base to apex. Microscopic section taken from this right lower lung area.

PATHOGENESIS

Proof of the actual pathogenesis of the various types found in the conditions under discussion rests with the pathologists. Briefly, the following summary may be offered:

1. In oil aspiration pneumonia, with mineral oil in some form being the offending agent, there is a foreign body aspiration reaction. Mineral oil is a bland hydrocarbon.

FIG. 10. (Case 2.) Microscopic section from right lung showing the typical oil drop deposit in the alveoli and in the septa. Note also the round cell infiltration and fibrosis. No giant cells were found in this slide.

Fig. 10. (Case 2.) Microscopic section from right lung showing the typical oil drop deposit in the alveoli and in the septa. Note also the round cell infiltration and fibrosis. No giant cells were found in this slide.

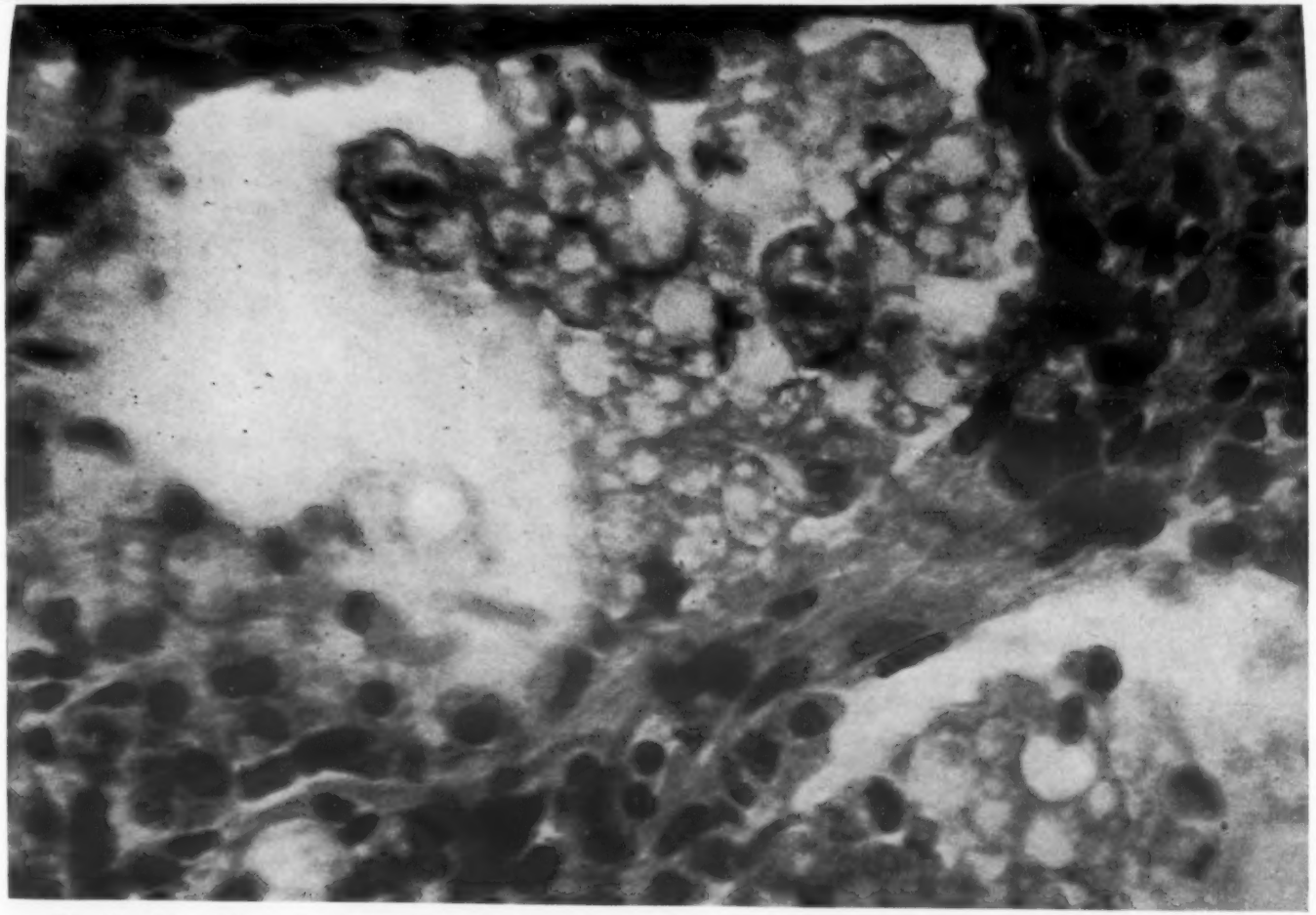


Fig. 11. (Case 2.) Higher magnification of figure 10, showing free oil droplets and oil-laden phagocytes in the alveolar spaces and also in the septal tissues. In some cases the nucleus has been pushed to one side and is crescent shaped giving the oil-laden cell a "signet ring" appearance. Here and there are seen the large mononuclear macrophages that have not as yet taken up the oil, one at the edge of the alveolar lining and another in the right field of the septum separating the two alveoli. Note the low cuboidal alveolar lining cells. The oil stained positively with Scharlach R.

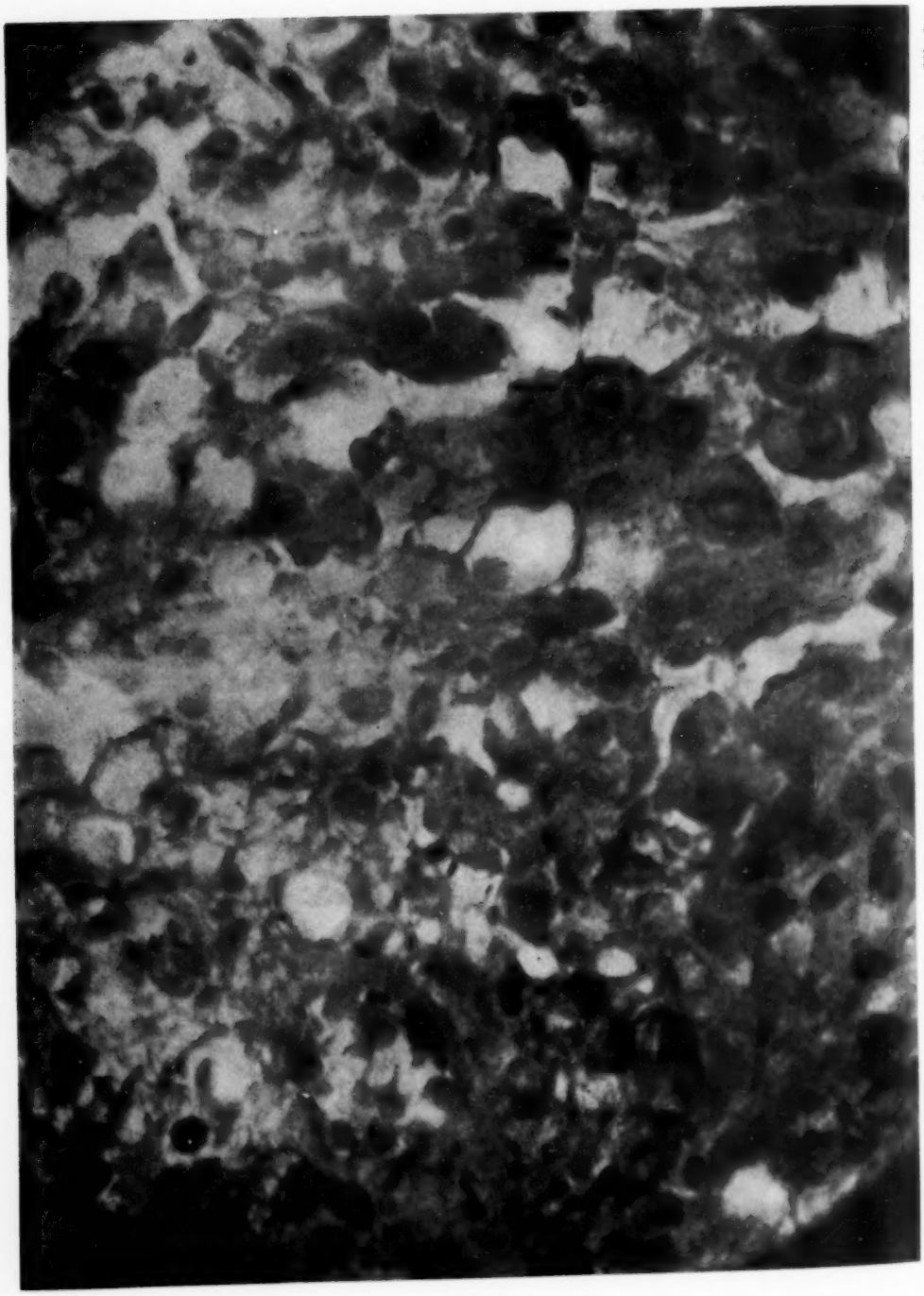


FIG. 12. (Case 3.) Microscopic section shows fat droplets and large mononuclear macrophages some of which are filled with the lipoid. A few "signet ring" cells will be not d. This section stained positively with Scharlach R.

It distributes itself finely dispersed. When placed in the mouth, pharynx, trachea or nose, the opportunity for insidious aspiration under conditions favoring this accident readily occurs. Usually no harm is done because respiratory movements, ciliary actions, and reflexes leading to coughing and clearing of the throat, rid the respiratory channels of the oil. However, in the absence or diminution of these defensive mechanisms the oil may reach and fill the alveoli and in so doing may produce a pneumonic process by:

a. Carrying infection down into the finer lung structures [65];
b. Blocking bronchial drainage and trapping oil and bacteria;
c. Lowering local resistance to bacteria (by devitalizing the cells).

In surviving cases, there is a gradual resolution of the pneumonic process with a stationary, residual fibrosis. There is perhaps a partial removal of oil by resumption of bronchial drainage in small amounts taking place over a period of time—and by migration of the oil phagocytes into the lymphatic channels.

2. In pneumolipoidosis of exogenous nature, the processes are probably similar except that here, in addition, hydrolysis and absorption take place, furthering the clearing of the lesion, leaving a residual fibrosis as in the oil cases. In addition the pulmonary damage done may be partly caused by the action of bacterial lipase on the offending lipid. (Suggested by Pinkerton.)

3. In pneumolipoidosis of endogenous nature, the fat deposition and accumulation in the lung depend on the underlying cause, which is in some instances partly known—as in:

a. Certain alveolar exudates of long standing (from cell degeneration in chronic pneumonic or suppurative pulmonary conditions). (Compare with Permar [73]);
b. Certain types of hepato-splenomegalic disorders: Gaucher, Nieman-Picks, etc.; or, in the special form of splenomegaly and lipoid-histiocytosis reported by Bloom [6] (cited by Pinkerton), with foam cells found in the lung, spleen, thymus and other organs;
c. The pulmonary manifestations of Hand Schüller-Christian disease, reported by Rowland,[89] and Sundelius [99] (of 63 cases, 14 showed pulmonary involvement—22 per cent);
d. Certain cases of lipemia (Houck [51]).

The pneumolipoidosis of endogenous nature may ultimately be found to be: (1) Different manifestations on the basis of an underlying systemic lipoid dyscrasia; or, (2) Different clinical entities on the basis of an imbalance of oxidase and lipase cell metabolism.

Phagocytes

The origin of the large mononuclear phagocyte is still under discussion. An endothelial origin (from blood and lymph vessel lining cells) is favored by Mallory,[68] Permar,[73] and Haythorn.[48] Briscoe,[11] Sewell,[94] Guieysse-Pellissier,[42] and Fauré-Fremiet [28] favor the opinion that these cells are derived from alveolar lining cells (of mesenchymal origin). A third group, MacCallum,[67] Delafield and Prudden [23] believe that cells of both origins occur. Pinkerton [78] believes that the alveolar phagocytes are macrophages of the same origin as macrophages in other organs; that they are specialized endothelial cells, histiocytes and blood monocytes. They do not come from ordinary vascular endothelium. Westhues,[106] in an admirable paper report-

ing his experiments, concludes that both endothelial and alveolar lining cells, and to some extent histiocytes, are the original cells from which are derived the large mononuclear phagocytes found in the lung.

Prophylaxis and Treatment

These headings are purposely grouped together as it may be justifiably stated that the best therapy is prevention. Bearing in mind the vast opportunity for insidious aspiration of oil or lipoids through the life of a civilized man, the relative rarity of the disease is apparent. Rather than to condemn or ban the use of oil or lipoid agent medication or to limit food intake to that of low fat content—both tasks that are practically speaking impossible—it becomes the duty of every doctor to impress upon his patients that care and common sense should be practiced in the use and in the method of administration of oil and lipoids.

As most doctors will have found upon inquiry, no harm is done provided the patient is in good general condition and provided self-administration is carried out under correct instructions or medical supervision.

When an agent is prescribed, the following suggestions are of value:

1. The agent preferably should not be administered before retiring. The material may trickle down into the trachea and bronchi and insidious aspiration may occur in this fashion during sleep.
2. When the patient is confined to bed, flat on his back, utmost caution should be exercised in the amount, frequency, and duration of administration.
3. In cases of subdued or absent reflexes from whatever cause, substitution therapy should be used and oil and lipoid agents abolished. They should be abandoned during the presence of symptoms favoring aspiration. This is particularly true in severe debilitating diseases and those conditions affecting the normal reflexes of the throat and of deglutition.
4. In suspected cases of pneumolipoidosis, iodized oil for bronchographic purposes should be deferred as a process that may add insult to injury in spite of the fact that the vegetable oil base in iodized oils is relatively harmless.
5. In infants with conditions favoring aspiration it is best to use fat free formulas.

There is no specific treatment known. The main therapy consists of adequately treating the associated disease or disorder. If the diagnosis is suspected early, during the period of administration, perhaps discontinuance of the agent and postural drainage may be beneficial—at least as a preventive measure. At a later stage, by the nature of the disease, postural drainage is a useless procedure.

Bronchoscopy as a therapeutic measure is of little value. In the early cases, there may be free drainage; in the later stages the lesion is beyond the reach of the bronchoscope.

Radio-therapy has been used in several cases but this should rather be warned against as it may augment existing fibrosis.

Activity should be reduced to conform to the disability resulting from the pulmonary involvement. Passive respiratory exercises may perhaps be tried. The more strenuous forms (blow bottles) are best avoided as ineffectual with regard to the fibrosis and are probably further debilitating in producing or increasing emphysema and possibly leading to right heart strain or failure.

So much for pneumolipoidosis of exogenous nature. Rational therapy of pneumolipoidosis of endogenous nature, except when the underlying cause may be known, must await further development by biochemists and pathologists of knowledge of lipoid metabolism that may indicate the pathogenesis of the disease entities in this group.

Prognosis

The usual cause of death is the accompanying disease or disorder. The prognosis in an uncomplicated case is usually good, leaving the patient with a varying degree of pulmonary fibrosis and with a corresponding limitation in his activities, but not such usually as to preclude the average normal activity.

Case Reports

Case 1. A white man, aged 40, bank employee. First admitted to St. Luke's Hospital September 1936. Onset of the present illness dates back to 1928 when patient began to receive treatments for sinusitis. Had been using a paraffin oil base spray at least three times a day, one application always at night before retiring. This procedure was followed over a period of eight years.

In the same year, 1928, he had several operations with removal of turbinates and sub-mucous resection in addition to treatments and irrigations of ethmoidal, sphenoidal and antral sinuses.

He was in general good health except for three or four sinus flare-ups during the year, accompanied by fever up to 102° F., lasting three to seven days. He was conscious of occasional post-nasal drip. He was able to attend to business regularly with the exception of the few days during these acute flare-ups.

In May 1935 the patient was aware of fatigue, suffered some loss of weight (4 or 5 pounds) and felt generally run down.

In January 1936 he had what he thought was another sinus flare-up. It started with a "grippy" feeling which progressed into prostration with chills and fever up to 105° F. The sinus irrigations were clear at this time. Dr. Adams at Katonah, N. Y., believed the patient had pneumonia or a bronchopneumonia of an unusual type inasmuch as he had no cough, expectoration, hemoptysis, chest pain, dyspnea or palpitation. With no sputum available, a pneumococcus typing was not done. There was a numerical variation in leukocytes that was not diagnostic.

The patient recovered in 26 days but felt too tired to resume work until May 1936. He worked for a few days and then began to run a low-grade fever again, 101° F., which continued for about a week with occasional nausea, vomiting and exacerbation of sinusitis. He failed to gain and now noted dyspnea after moderate exertion.

Dr. Adams at this time (September 1936) suspected an oil aspiration pneumonia and referred the patient to the Medical Service of Dr. Lewis F. Frissell at St. Luke's Hospital. Roentgen-rays taken in May, July and September of this year were briefly interpreted as unresolved lesions of the lung with little change noted in the series of pictures.

On admission to the Hospital the patient was a well-developed and well-nourished man and did not appear acutely or chronically ill. The positive findings on physical examination were: Temperature 99° F.; weight 138; diminished resonance below the ninth rib posteriorly on the left, with fine moist râles at the posterior left base and in the left axilla to the anterior axillary line. Breath sounds and voice were normal. There was a slight diminution of resonance below the right clavicle; blood pressure was 120 systolic and 70 diastolic and pulse 88. There was a slight dorsal scoliosis; moderate sized hemorrhoids were found.

Nose and Throat Consultation: Left middle turbinate removed; right middle turbinate partly removed; ethmoidal and sphenoidal sinuses were clean; on irrigation, both antra gave clear returns; tonsillar re-growths in both fossae; rest of the examination negative.

Roentgen-Ray Examination: The chest plate showed the heart, aorta and diaphragm to be normal. The left lung field revealed consolidation involving the lower half of the lung. On the right there was a consolidation extending from the lower pole of the right hilum down to the diaphragm and out almost to the periphery. Compared with the former films, the right sided lesion appears stationary; the left, however, more extensive. (Figures 6 and 7.) Roentgen-ray of the sinuses showed chronic mucosal thickenings of both antra. The other sinuses were clear. Electrocardiogram showed a relatively normal tracing. Vital capacity was 81.4 per cent (September 1936). Other laboratory findings were essentially negative.

Urine negative; Wassermann and Kline tests negative; urea N 14.7 mg. per cent; sugar 100 mg. per cent; CO_2 51.9 volumes per cent; stool negative; malaria-hunt negative; hemoglobin 100 per cent; red blood cells 5,000,000. The leukocytes were 7,800 with 68 per cent polymorphonuclears; 28 per cent lymphocytes; 4 per cent transitionals. The count rose to 13,000 with a subsequent drop to 10,000 without increase in the polymorphonuclears. Sputum was negative for tubercle bacilli on three occasions. Free oil droplets were found in the sputum examination twice on consecutive days although no cellular elements were found. The patient had no expectoration so these specimens were obtained by clearing the throat in the morning on arising.

Treatment: The patient was on bed rest with a regular diet. Until the oil droplets were found in the sputum he received four nightly doses of mineral oil (oz. 1). He had no complaints and slept well and was discharged from the hospital in October 1936, after 11 days.

He returned under the care of Dr. Adams with occasional visits to Dr. Forbes of New York, for checks on his sinus condition; Dr. Forbes also made a bronchoscopic examination without any positive findings. Nothing was seen from which a biopsy specimen could be obtained. No abnormal secretions were found. The bronchi were patent and normal in appearance. A suction specimen from the lower bronchi revealed no visible fat droplets.

Upon recommendation the patient went to Arizona for four months. There were no constitutional or respiratory symptoms during this period except for the following: Weakness and fatigue, mild dyspnea on moderate exertion, pulse elevation to 126, occasional low-grade fever 99° F. to 99.2° F., elevation of blood pressure to 140 systolic and 90 diastolic; weight remained stationary. The vital capacity was now 79 per cent six months after the first estimation was done. Examination of the lungs revealed dullness at the left base extending to the left axilla with harsh and loud breath sounds and prolonged expiration. There were numerous medium to fine moist râles. On the right side there were occasional moist râles in the axilla and at the

level of the scapular angle. Roentgen-ray examinations remained unchanged. A bronchogram with iodized oil was suggested to rule out the possibility of bronchiectasis but was not done.

Upon return (June 1937), the patient submitted to hospitalization at St. Luke's Hospital for a check-up. He still complained of lassitude, fatigue and mild dyspnea on exertion. He was afebrile, had a normal pulse rate, and except for a moderate elevation of the white blood cells, the blood picture was normal and the blood chemistry unchanged. Sedimentation rate at this time was 19 mm. in one hour and the blood cholesterol was 222. Sputum was not produced spontaneously but a five day specimen collected by forced morning cough was negative for fats by stain, and a section made from blocked concentrated sputum sediment showed only a small amount of débris but nothing that would take the fat stain. Postural drainage produced no bronchial elimination. The gastric contents concentrated for tubercle bacilli were negative. A chest roentgen-ray taken at this time, June 1937 (figure 8), showed no change. Since the last discharge, June 8, 1937, the patient has remained at home. When last heard from, May 1938, he was still complaining of lassitude, fatigability and dyspnea on mild exertion.

This case is reported as representative of oil aspiration pneumonia in a living adult.

Case 2. This is a white man (Jewish), aged 60, storekeeper. Admitted to the Neurological Service of Dr. R. G. MacRobert and transferred to the Chest Service of Dr. G. Thorburn at Lennox Hill Hospital in September 1936. Onset of the present illness dates back to 1925, when the patient had a sudden loss of consciousness and a left hemiplegia. There was gradual improvement and the patient was soon able to walk about. In 1931 the patient found he was unable to talk and had difficulty in swallowing. He was unable to protrude his tongue and noticed inequality of facial musculature. There was again gradual improvement. The patient had a fear of being alone and of entering subways. At one period, dysphagia was such that he had to be fed through a stomach tube. He showed a gradual loss of weight. Four weeks prior to demise the patient had a slight cold which incapacitated him totally. He grew very weak and, although he tried to cough, was unable to expectorate. He ran a continuous elevation of temperature. He felt more comfortable in the orthopneic position. With his cough and fever, he also had headaches, vertigo, occasional vomiting and fainting spells.

Checking the history, the following information was obtained from the widow in March 1938: The patient had been very constipated for the 11 years preceding his death and over this period of time took one tablespoonful of mineral oil every night, using thus many quarts of it as a laxative. At times, this medication was alternated with other laxatives, cascara, milk of magnesia, pills, etc., up to two weeks before death. He had never used nose drops or sprays. The patient's history included the usual childhood diseases (measles, mumps, whooping cough, colds, tonsillitis), and he always had had a slight non-productive cough. He had urgency and frequency of urination.

On physical examination, the patient was thin to emaciation. The temperature was 103° F. and the pulse 100. The patient had difficulty in breathing. Examination of the chest revealed dullness at the right base, and a general scattering of mucous râles over both lungs, finer and more distant over the right base. Vocal fremitus was conserved throughout. Heart examination was unsatisfactory due to over-lying mucous râles. Blood pressure was 108 systolic and 68 diastolic. Generalized weakness with slight muscular atrophy and loss of strength was found particularly marked on the left side. Teeth were in very poor condition. He was unable to move his tongue which was found flabby to touch. Pharyngeal reflexes and palatal movements were absent. Sense of touch in the posterior pharynx was present but diminished compared with the touch sense of the buccal cavity membranes. Dysarthria was

found. The speech was stammering and stuttering. Test phrases were impossible. Equilibratory tests were well performed. The handwriting was good. The deep and superficial reflexes were present and active. Abdominal reflexes were absent. No abnormal reflexes elicited. No signs of meningeal irritation, no sensory disturbances, no disturbance of stereognosis, baragnosis or topognosis. The pupils were equal but did not react to light; the right pupil was larger than the left. Fundi showed slight arteriosclerotic changes on the right. Examination of the other cranial nerves revealed poor subjective and objective taste. Movements of the facial muscles were impaired on the left. Poor articulation of labials. Absent pharyngeal reflexes bilaterally; impaired swallowing; impaired movements of tongue with inability to protrude it. Subsequent examination of the chest revealed signs indicative of thickened pleura with or without fluid in the right chest. Fluoroscopic and roentgen-ray examination of the chest showed areas of dense triangular shadowing below the right hilum and pleural effusion with at least three fluid levels, one of these levels half way up the thorax. Generalized thickening of the pleura on the right side and patch consolidation shadows on the left lower lung field. The roentgen-ray was interpreted as a pneumonic process of the right lower lobe with possible collapse of the right lower lobe with over-lying effusion or pus and a hypostatic bronchopneumonic process on the left (figure 9). Several taps were attempted, finally producing thick, green, foul pus and tube drainage was instituted.

Laboratory examinations revealed a leukocytosis of 16,900 white cells with 96 per cent polymorphonuclears. The blood chemistry was negative (Urea N 12.7, creatinine 0.5, uric acid 2.7, and sugar 142 mg. per cent; CO_2 56.7 volumes per cent). Urinalyses showed some albumin and occasional hyalin casts. The chest fluid showed no growth in anaerobic or aerobic cultures. The patient ran a septic temperature from 101° to 103° F. with a terminal rise to 105° F. The nurses' notes revealed the fact that the patient was unable to expectorate. He showed great difficulty in swallowing even sips of water and choked at times on ingestion. He developed a decubitus ulcer over the coccyx. No oil or lipoid agent was administered during hospitalization.

The patient died October 12, 1936.

The autopsy, excluding head examination, was made the following day. The anatomical diagnoses were: Encapsulated empyema, right pleural cavity; interlobar abscess of right lung; diffuse bilateral bronchopneumonia; generalized arteriosclerosis; coronary sclerosis; dilatation of right ventricle; chronic passive congestion of liver; chronic passive congestion and fibrosis of spleen; renal arteriosclerosis; dilatation of stomach; and decubitus ulcer. Cause of death: Diffuse bilateral bronchopneumonia and arteriosclerotic cardiorenal disease.

The examination of the thorax revealed 150 c.c. of turbid yellow serofibrinous fluid in the left pleural cavity with a few pleural adhesions to the diaphragm. Section revealed yellow-gray consolidation of left lower lobe and lower half of left upper lobe. The right lung was adherent everywhere to the chest wall. Upon breaking through the adhesion a large cavity was revealed over-lying practically the entire right border of the lung. The cavity contained a moderate amount of green-yellow pus. Upon removal of the lung, a second small cavity was found; both cavities were encapsulated. The parietal pleura was greatly thickened and leathery in quality. The empyema did not perforate the parietal pleura. A third abscess about 3 cm. in diameter was located between the upper and middle lobes and was separate from the empyema cavities. There was pus in the upper right bronchus. The lower and middle lobes were firm and on section revealed yellow-gray consolidation.

On microscopic examination, the following note was made: "Lungs: Congestion and infiltration with small round cells and polymorphonuclears. The lung presents a peculiar foamy appearance as if the alveoli and interstitial tissues contained a great deal of fat. (Figures 10 and 11.) When stained with Scharlach R, this is demon-

strated to be the case." (This slide was not preserved.) The liver showed moderate congestion and numerous focal areas of fatty degeneration. The spleen was interpreted as chronic splenitis with deep congestion and fibrosis. (No foam cells were seen.)

This case is reported as representing oil aspiration pneumonia with autopsy findings. The fact that no paraffinoma or giant cells nor extensive gross fibrosis were found in spite of 11 years' administration of oil may be explained on the basis of insidious aspiration of small amounts of oil over a long period. Massive accumulation may have been prevented by the cough reflex. Although the patient was unable to expectorate, he probably raised the oil to the pharynx and swallowed it. Perhaps a more likely explanation is that the aspiration of the oil took place during the shorter period (four weeks) of his last illness prior to admission to the hospital.

Case 3. White, male infant, eight days old, admitted to St. Luke's Hospital, Pediatric Service of Dr. Elmer F. Johnson because the parents noted symptoms similar to those of a brother, five months of age, who had died one year previously with amyotonia congenita. The child had had no other illnesses, was breast-fed for two days and since then had been on bottle feeding. (Formula not stated.)

The patient showed good development and nutrition and weighed 8 lbs. 10½ ozs. It was noted that the patient had a weak cry, had jerky respirations and was lying motionless. The musculature was flabby, spine poorly supported when picked up; the fontanels were open and there were cephalo-hematomata of the parietal regions; knee jerks were not obtained and there were no plantar reflexes. A biopsy from the right gastrocnemius muscle led to the diagnosis of amyotonia congenita.

The routine laboratory examinations and skin tests were negative except for a leukocytosis of 13,300 with a relative lymphocytosis (62 per cent lymphocytes).

Subsequent examinations revealed a cretinoid appearance with a rather large tongue. Skeletal muscles were weak, particularly the spinal group, and the baby did not move the extremities; fontanels and sutures were wide open. The chest was flattened laterally with an outward flare at the base, but the lungs were clear throughout hospitalization. The child did not take feedings very well and occasionally vomited and regurgitated the evaporated milk formula. During these episodes the vomitus was apparently aspirated as the baby turned very cyanotic and stopped breathing. The foot of the bassinet was elevated in an attempt to prevent aspiration. Examination of the throat was negative so it was believed that the difficulty in swallowing was due to the general condition. The infant was afebrile during the period of hospitalization. Symptomatic treatment, regulation of feeding, and thyroid extract did not result in any improvement.

The final note reads as follows: "For the past three weeks, the baby has had jerky respirations and periods of being cyanotic and at times is gray in appearance, and has been constantly so the past three or four days. During the last 24 hours the baby vomited some of the feedings and had severe attacks of deep cyanosis and periods of cessation of breathing. He died during one of these attacks on the twenty-fourth day of hospitalization."

An autopsy was done eight hours post mortem. On opening the chest, no fluid was found in either pleural cavity. The pleural surfaces were smooth throughout. The upper and lower lobes of the right lung were non-crepitant and on section had a deep red-gray appearance. The trachea and bronchi of both sides contained coagulated milk curds. The liver was enlarged. Cut section showed no gross abnormalities. Spleen was normal and two small accessory spleens were present. Mesenteric lymph nodes about the celiac axis were enlarged and soft. No gross abnormalities were found in any of the other organs including the brain. The anatomical diagnosis was: Amyotonia congenita and bronchopneumonia, right upper and lower lobes.

Microscopic examination of the lungs showed collapse of many of the alveoli while others were filled with desquamated swollen septal cells, monocytes, blood and

serum. Other alveoli were filled with polynuclear cells in areas scattered about the vicinity of the bronchioles. Scattered through portions of the lung were areas which showed free droplets and large mononuclear cells. Many of these mononuclear cells showed fat droplets, some of them completely filled, producing the typical "signet ring" effect of fat replaced cytoplasm with peripherally placed and flattened nucleus. This section stained positively with Scharlach R (figure 12). The liver showed some congestion of the sinusoids in the region of the central veins. The medulla of the adrenal showed a dense supporting tissue with areas of fatty degeneration. The anterior and posterior columns of the spinal cord in the cervical, thoracic, and lumbar regions revealed a paucity of ganglion cells which, however, appeared normal in architecture. Muscle sections revealed minute muscle cells perfect in structure but diminished in size, alternating with normal or slightly hypertrophied cells.

Microscopic diagnosis: Amyotonia congenita; bronchopneumonia.

This case is reported as representative of pneumolipoidosis of exogenous nature.

Case 4. Male infant, 23 months old, white, admitted to St. Luke's Hospital August 27, 1934, to the Pediatric Service of Dr. F. Elmer Johnson, with a history of moderate fever for five days.

The child was listless and apathetic and had vomited on one occasion only. One dose of castor oil had been given for constipation at the onset of the illness five days before. The baby took all its feeding poorly.

The past history revealed that the baby had cod liver oil at the age of three months. The amount and the duration were not stated but it was stopped because of vomiting.

On examination the baby appeared acutely ill and was very irritable. Shallow respirations and occasional cough were noted.

Examination of the chest revealed dullness, broncho-vesicular breath sounds and a moderate number of moist râles over the right lower chest. There were slight rosary nodes in the ribs.

Roentgen-ray examination revealed consolidation of the lower outer two-thirds of the right upper lobe which on subsequent examination extended through the whole right upper lobe and right middle lobe (figures 13 and 14). During his stay in the hospital the baby became more apathetic, listless and exhausted. There was a low-grade fever, from 98° F. to 101° F., with a disproportionately high pulse rate. Bilateral otitis media developed necessitating myringotomies. From the varying physical signs the clinical impressions were listed as bronchial pneumonia, localized pneumothorax, right lung abscess and fibrotic lung. Neurological signs developed which at the time led to consideration of a brain abscess, frontal lobe involvement. The child was fed by Levine tube for 16 days. However, he was fed fluids without milk or other fat substances and later on 50 per cent protein milk alternating with liver juice. Only once was mineral oil ½ oz. given through the tube.

The nurses' notes state that the Levine tube and the feedings through it were taken rather well without vigorous effort to remove it. The child was variously described in the nurses' notes as being irritable, nervous, toxic, coughing, and, without the Levine tube, would present a definite feeding problem. Fluids were poorly taken due to restlessness, crying or coughing, or else were refused entirely or taken only with forcing. The stomach was lavaged every three hours prior to feeding. The child gradually lost ground and died on the thirty-first day of hospitalization with a terminal temperature of 103° F. and a pulse rate of 156.

The autopsy was performed within 12 hours of death. The body was definitely undernourished but well developed. There were no palpable lymph glands. The right lung was heavy, 175 grams, and adherent to the diaphragm and to the posterior lateral chest wall.

On section of the right lung numerous cavities from 0.5 to 1.5 cm. were found containing thick creamy purulent fluid. The confluent areas consisted of saccular

dilatations of the small bronchi whose walls were fibrous and non-collapsible. The surrounding lung was closely packed with confluent, pale, firm, consolidated granular areas and bronchopneumonic infiltration. The left lung weighed 75 grams, was moderately congested and showed a fresh infarct 1 cm. in diameter. The liver was markedly enlarged (600 grams), pink, soft, with a very greasy cut surface. The spleen was soft, edematous and slightly congested and showed distinct lymphoid markings. There was slight hypertrophy of Peyer's patches and the mesenteric nodes were enlarged, soft and slightly congested.

FIG. 13. (Case 4.) Chest roentgen-ray of case reported for discussion taken on day of admission showing a maximum pneumonic involvement of the lower lateral portion of the right upper lobe.

Anatomical diagnosis: Right suppurative bronchiectasis with multiple abscess cavity formation; right bronchial pneumonia with pleurisy; infarct left lung; cerebral congestion and edema; fatty degeneration of the liver and healed rickets.

On microscopic examination, the section of the right lung showed large monocytes in the alveoli which stained positively with Scharlach R. Other alveoli were filled with Scharlach R stained droplets and cellular elements. Scharlach R stained fat was also found in the septa intracellularly. In some areas there was confluence of the stained droplets. Infrequently fine concentric staining was seen in parts of the capillary wall. Definite cuboidal alveolar lining epithelium was found here and there. There was much round cell infiltration, sometimes perivascularly, and at times packing

alveoli with an interspersion of Scharlach R stain. In the areas thus involved there was a fine fibrosis and a teased out appearance of the stain. No stain was found in the blood vessels, bronchioles or bronchi (figure 15).

In the follicular centers of the mesenteric lymph node a few large mononuclear cells were occasionally seen with large pale nuclei and pink cytoplasms (H. and E. stain). A rare vacuole was seen now and then only. In the liver the parenchymal cell cytoplasm was entirely replaced with large discrete droplets. The cells were filled or distended with fat (vacuolated), pushing the nucleus to the periphery and flattening it in many instances.

The other microscopic findings are omitted for the sake of brevity.

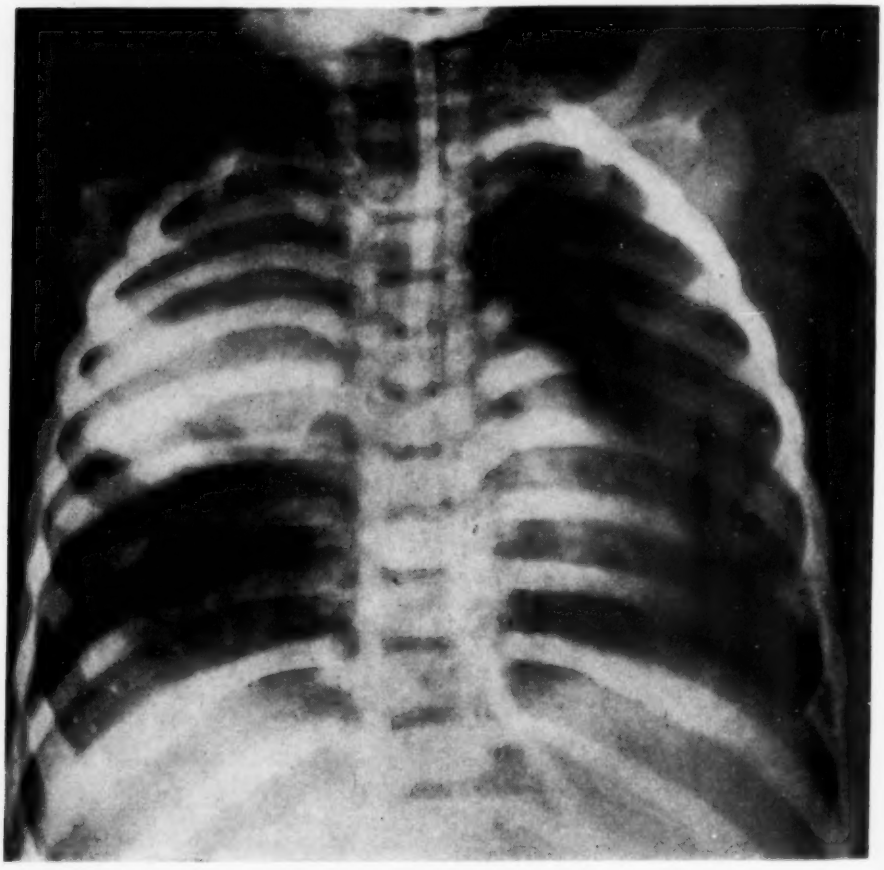


FIG. 14. (Case 4.) Roentgen-ray taken four days later showing an increased involvement of the right upper lobe and the Levine tube in situ.

This case has not been included in the above summarized series of cases but is reported separately for discussion of diagnosis. Several "diagnostic features" favoring the diagnoses under discussion are presented:

1. One-half ounce of mineral oil given during hospitalization through Levine tube.

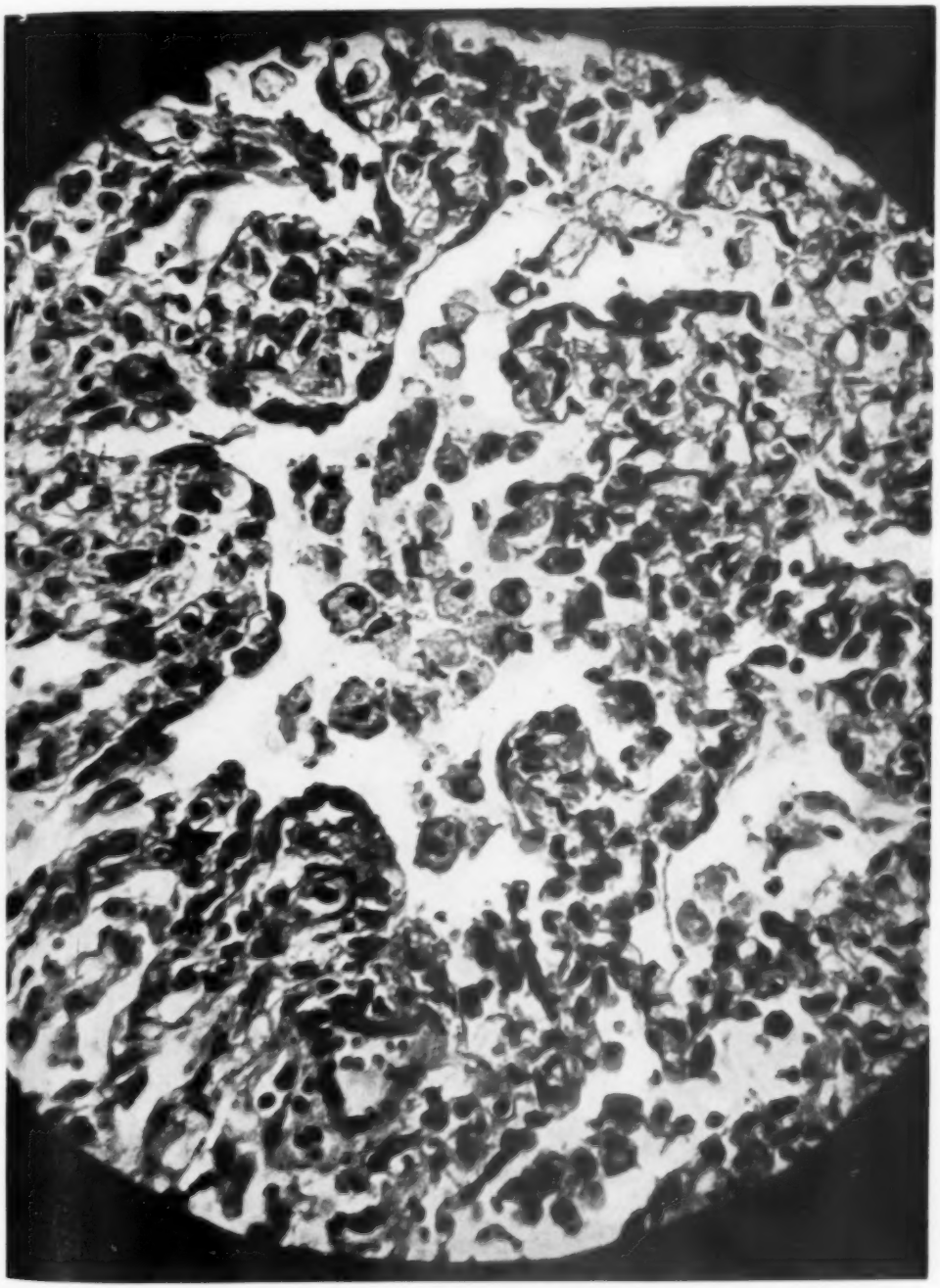


FIG. 15. (Case 4.) Microscopic section. Note large mononuclear cells in alveolar spaces. Also in the septal tissue (upper right field). Several of these mononuclear cells show vacuoles either from phagocytic activity of exogenous lipoid or from fat deposit by disturbance in oxidase lipase cell metabolism. Note also alveolar cuboidal lining epithelium. The monocytes and phagocytes here seen stain positively with Scharlach R.

2. One dose of castor oil given at onset of illness, five days before admission.
3. Cod liver oil had been given at the age of three months.

Several conditions favoring aspiration are presented: Listlessness, apathy, vomiting, irritability, cough, neurological signs, feeding difficulty, and Levine tube feeding with lavage every three hours.

Physical signs and chest roentgen-ray examinations although not "typical" do not preclude the diagnosis under discussion. The complicating otitis media and pneumonia (bronchial) are supporting diagnostic factors. The gross pathologic examination does not reveal any typical picture. The microscopic examination of the involved lung, however, does show large phagocytic monocytes some of which have enclosed fat- (or oil-) staining droplets. There is evidence of transition of alveolar lining cells to the low cuboidal type. Fibrosis is also present. On the basis of the above, it may be questioned whether this is a case of early reaction to mineral oil (oil aspiration pneumonia), or an endogenous accumulation of cell lipoids following a prolonged chronic pulmonary infection (pneumolipoidosis of endogenous nature).

Summary

Review of 136 Cases Mentioned or Reported in the Literature

The terms oil aspiration pneumonia and pneumolipoidosis are suggested as covering the various phases of this clinico-pathological entity. The disorder is relatively rare in occurrence but conservatism in statistics is recommended until a larger series of fully reported cases is available. The clinical diagnosis is not based on any distinctive features but on a combination of facts:

1. A definite history of the use of an oil or lipoid agent.
2. The presence of symptoms or conditions favoring aspiration, especially important where lipoids of food may be the offending agent.
3. Symptoms are mainly those of associated diseases or disorders which are most frequently found to be respiratory tract infections and other infectious diseases, central nervous system disorders, impaired general condition, and feeding or swallowing difficulties. Usually there is a combination of two or more of these disorders.
4. Physical examination reveals no specific signs. There is usually some degree of nutritional disturbance. Rapid respirations are frequently recorded. Fever, if present, is usually low-grade and the chest signs are those of the usually associated respiratory infection.
5. The roentgen-ray is of the greatest diagnostic value but may often be difficult to interpret due to other pulmonary diseases. A lack of change over a long period of time in serial chest roentgen-rays is an important point.

6. Sputum examination for free oil droplets or large phagocytic monocytes containing fat or oil should always be done in suspected cases.
7. Interval vital capacity estimations are recommended.

The gross and microscopic pathology is briefly described.

Final diagnostic proof is obtained by identification of the offending agent by chemical analysis of the oil or lipoid in the involved lung tissue. It is further recommended that scrapings from the cut surface of lungs in all cases of lung examinations be streaked and stained for fat at the time of autopsy. If the above test is positive, qualitative and quantitative chemical analysis for fats should be done.

The pathogenesis of oil aspiration pneumonia and pneumolipoidosis of exogenous nature and pneumolipoidosis of endogenous nature is briefly touched upon.

The best therapy is prevention. Recommendations on prophylaxis are made. The treatment is mainly that of the associated disease or disorder.

Prognosis is dependent upon the accompanying disease or disorder. In uncomplicated cases, the prognosis is good.

Four cases are reported.

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THE DIAGNOSIS OF POLYCYTHEMIA *

By WILLIAM DAMESHEK, M.D., and HENRY H. HENSTELL, M.D.,†
Boston, Massachusetts

POLYCYTHEMIA vera is a relatively "new" disease. Although first described by Vaquez [1] in 1892, it did not become generally known until after the appearance of Osler's articles in 1903 and 1908.[2, 3] Since that time, it has usually been considered a rarity; evidence for this is present in the very few references to the disease from year to year in the world's literature. Among the various hematological conditions listed in the Quarterly Cumulative Index Medicus, polycythemia ranks close to the last. Even in the last few years, with the evident great interest in the various disorders of the blood, the number of references per year for this disease is small.

The rarity of this disease may be more apparent than real. In the last nine years, at a relatively small hospital (about 200 beds), we have had the opportunity of studying at least 20 cases; in the past two years alone, 11 new cases have been seen. Since the diagnosis of polycythemia had not been suspected in several of these cases until after years of observation by many physicians, it is possible that the apparent rarity of the condition is at least in some measure due to its lack of recognition. The purpose of the present paper is to point out certain prominent symptom-complexes of the disease. At times, these may be so outstanding as to lead to an erroneous diagnosis. Analysis of our cases suggests that data leading to a correct diagnosis can usually be obtained from the history and physical examination. Careful consideration of the laboratory findings has further led to criteria for the establishment of a definite diagnosis of the condition and for differentiating the doubtful from the true case of polycythemia.

The symptoms of polycythemia are in all probability due to great overloading of the entire circulation with blood with resultant sensations referable to the head, the cardio-vascular system, the gastrointestinal tract, and the extremities. In some cases, a great multiplicity of symptoms is present with the result that neurasthenia may be diagnosed; in most cases, however, emphasis is placed by the patient on one bodily system or another.[4] In these, such diagnoses as migraine, brain tumor, and peripheral vascular disease may be made. In the following case reports, emphasis is placed upon the great differences in symptomatology from case to case.

A. Cases with "Peripheral Vascular Disease" Outstanding. In these three cases, the outstanding feature for two to six years was a marked disorder of peripheral blood vessels. It is possible, to be sure, that the vascular

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From the Medical Service and Hematology Laboratory, Beth Israel Hospital, Boston.
† Charlton Fellow in Medicine, Tufts College Medical School (1936–37).
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disorder bore no relationship whatever to the polycythemic state or that a "primary" disorder such as thromboangiitis obliterans might secondarily result in polycythemia through the development of vascular changes in the marrow (Reznikoff et al.[5]). This might conceivably have been the state of affairs in the first case of this group (Maurice G.). In the second case (Nathan W.) the lack of large vessel involvement, and the extremely high platelet count in the presence of relatively slight elevation in the red cell count suggest the possibility of "platelet polycythemia" or "thrombophilia" with multiple small peripheral vascular thromboses.[6] In the third case (Dora P.) the diagnosis of erythromelalgia was entertained for years. Since the sensations of pain, warmth, and tingling of the legs are common to both polycythemia and the rather poorly defined disorder of erythromelalgia, the possibility of polycythemia should be suspected when the diagnosis of erythromelalgia is made. In any event, symptoms of peripheral vascular disease are common in polycythemia.[7]

Case 1. Maurice G., a 40 year old Russian-Jewish canary peddler, first entered the hospital on August 10, 1928 with mild left hemiplegia. In 1927 he had developed cramps in the right leg and a sensation of coldness in the right big toe. He soon noticed increasing difficulty in walking because of claudication in the right leg. At another hospital in August 1927 the distal half of the right big toe was found to be reddish blue and very tender to touch. The diagnosis of thromboangiitis obliterans was made and lumbar sympathectomy of the first, second, third, and fourth ganglia was performed with some relief. The red cell count at this time was recorded as 5.24 million. In August 1928 he noticed tingling sensations and jerky motions of the left arm and leg and in a few days developed paralysis of these extremities. At the Beth Israel Hospital at this time, the diagnoses of thrombophlebitis of the right leg and cerebral thrombosis with left hemiplegia were made. Because of the findings of splenomegaly and a slightly elevated erythrocyte count (hemoglobin 106; red blood cells 5.42 to 6.79 million) the possibility of polycythemia was considered. In November 1929, he complained of pain in the epigastrium radiating to the sternal region and down the left arm. It was felt that he was suffering from coronary thrombosis. At this time, the hemoglobin concentration was greater than 100 per cent, erythrocytes varied from 7.54 to 10.0 million, and the blood-platelet count was close to 1.0 million per cu. mm. In June 1930 the complaints of vertigo and headache were outstanding. The patient was now plethoric with reddish cyanosis of the lips; the tongue large and thickly coated; the mucous membranes congested; the liver edge felt four fingers' breadth, the splenic edge three fingers' breadth below their respective costal margins; and the erythrocytes elevated between 7.20 and 9.70 million per cu. mm. The urine showed a very slight to a slight trace of albumin. In 1932 the red cell count was consistently in the neighborhood of 10.0 million. Treatment with occasional venesections, spleen extract, Fowler's solution, roentgen-radiation of the bones, and phenylhydrazine were all tried at various times but without much relief. Finally, he refused to take medication and insisted on occasional venesections which gave temporary symptomatic relief. In 1933, 1934, and 1935 he had frequent spells of vomiting. In April 1935 severe hematemesis occurred, following which the erythrocyte count dropped from over 8.0 million to 4.2 million. A large gastric ulcer was found by roentgen-ray. For several months after this episode, and while on a Sippy regime, he showed a reduction in hemoglobin and an erythrocyte count between 5.0 and 5.5 million. The ob-

TABLE I

Analysis of Symptoms

	1 M. G.	2 N. W.	3 D. P.	4 S. S.	5 R. W.	6 J. G.	7 R. S.	8 G. F.	9 S. W.	10 F. R.	11 S. M.	12 C. B.	13 M. C.	14 G. M.	15 M. F.	16 R. G.	17 F. S.	18 M. A.	19 H. A.	20 S. C.
Headache	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Migraine			X								X	X								
Vertigo	X	X	X	X	X	X	X	X			X		X		X	X	X		X	
Visual (especially colored scotomata)						X							X			X	X	X	X	X (Conjunctival) nodules
Cardiorespiratory			X	X	X	X		X				X				X		X		
Abdominal pain	X					X			X	X	X	X	X		X			X	X	
Constipation	X	X	X	X		X		X	X	X	X	X	X			X	X		X	
Ulcer	X								X				X					X		
Paresthesias	X	X	X	X		X		X				X		X	X	X	X		X	
Extremities	X	X	X	X										X	X			X		
Bleeding tendency	X		X					X		X	X	X					X		X	
Thromboses	X	X	X	X	X	X		X				X						X		
Weakness	X		X	X		X										X	X	X	X	

TABLE II

Signs

Plethoric appearance	Every case				
Distended retinal veins	Every case				
Large, geographic tongue	1, 3, 6, 8, 11, 12, 13, 17, 19, 20				
Congested buccal mucous membranes	Every case				
Hepatomegaly	1, 2, 3, 4, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19				
Splenomegaly	1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 16, 18, 19, 20				
Vascular disturbances of the extremities	1, 2, 3, 4, 11, 18				
Blood pressure	1	2	3	4	5
	122/80	130/85	170/100	180/120 215/120	230/140
	6	7	8	9	10
	170/80	136/90	126/84	140/88	120/85
	11	12	13	14	15
	130/80	150/80	130/104	170/110	130/90
	16	17	18	19	20
	200/100	200/100	150/90	148/100	165/110

servations in this case following this severe hemorrhage were the basis for our use of the iron-deficiency regimen in the treatment of polycythemia.*

Case 2. Nathan W., a Russian born Jewish waiter, aged 45, came to the Medical Clinic of the Out-Patient Department on March 30, 1935, complaining of pain and blueness of the toes of both feet. Three years previously he had been examined at another hospital for pain and discoloration of the second toe of the right foot. The diagnosis of thromboangiitis obliterans was made and there was slow improvement with Buerger's exercises. In 1933, there was return of pain, burning, and cyanosis of several toes of the right foot with beginning gangrene of the third toe. He was treated with continuous dry heat and there was again gradual improvement. He managed to continue at work until February 1935 when the symptoms of pain and burning returned in the second toes of both feet and therapy with the Pavex boot was recommended. Examination in the out-patient department showed a plethoric man with a barrel-shaped chest. The liver edge was felt two fingers' breadth below the right costal margin; the spleen could not be felt. The distal halves of both feet showed red, blue, and violet discoloration with very slow blanching when the legs were raised. The dorsalis pedis and posterior tibial arteries of both feet were readily palpable. The blood pressure was 130 systolic and 85 diastolic. Routine laboratory data showed hemoglobin (Tallqvist) 85 per cent, and a negative urine examination. The diagnosis of thromboangiitis obliterans was made and the patient referred to the wards in April 1935 for further study and treatment.

It was concluded that he was suffering from arterial occlusion involving only the small blood vessels of the feet. The diagnosis of Buerger's disease was considered most likely, although Raynaud's disease was considered a possibility. Hematological studies showed: hemoglobin (Sahli) 115 per cent; red blood cells 7.00 million; white blood cells 18,900; and a marked increase in platelets as seen from the smear. The urine was negative. A platelet count done several days later was 2.85 million; further counts ranged from 3 to 6 million per cu. mm. (!). In view especially of the latter finding, it was felt that the primary disorder was polycythemia, the chief cellular element involved being the platelets rather than the red cells or leukocytes. The local changes in the small arteries were felt to be due to the extremely high platelet count and the consequent tendency to thrombosis together with increased viscosity of the blood incident to the elevated hemoglobin and erythrocyte counts.

Further studies confirmed these impressions: the percentage volume of the platelets (thrombocytocrit) was 3 (normal about 0.5 per cent); sternal bone marrow

* Appendix.

biopsy showed an extreme increase in megakaryocytes (which dominated the sections); roentgen-rays of the feet failed to show calcification of the arteries; the blood volume was 10,150 c.c. (120 c.c./kg.); and striking relief in symptomatology occurred when a venesection of 500 c.c. was instituted. However, this relief was short-lived and he complained of constant burning pain of the soles of the feet. In June 1935, the fourth right toe was the site of impending gangrene, the other toes being markedly cyanotic. The erythrocyte count was now 8.65 million. As no relief of symptoms occurred with heat and two venesections, he was transferred to an institution for chronic disease. Here he was given 1 to 2 injections of 300 c.c. of 5 per cent salt solution intravenously every week for about eight weeks with such striking relief in symptoms that he was able to return to his occupation as a waiter in January 1936. He has since been followed in the Blood Clinic, and has been kept symptom-free on an iron-deficiency regimen together with the occasional use of 5 per cent hypertonic salt solution intravenously.

Case 3. Dora P., a 57 year old Russian-Jewish housewife, was admitted to the hospital in 1932 because of severe constant pains in the legs which had begun about five years previously. For many years she had been troubled with excruciating headaches coming in spells every one to four weeks and always associated with severe vomiting. These severe intermittent headaches which were probably "migraine" disappeared suddenly at the time of the menopause. Since then, however, she frequently complained of a dull and more constant headache. She had also suffered from vertigo, weakness, backache, and since her menopause in 1925, from hot flashes. She had been told by several physicians that her symptoms were due to "high blood pressure" and "change in life." Symptoms referable to the legs had become the dominating feature in 1928. With walking, standing, or sitting (i.e. whenever the legs were in a dependent position) there was usually an unbearable "burning" sensation worse than the associated slight pain. The burning and pain were usually worse in hot weather and with hot baths and were greatly relieved by cold bathing. She had been treated for a few years for flat feet, varicose veins, etc. without relief. On admission to the Surgical Service (private) of the hospital in 1932, the diagnosis of erythromelalgia was made. Blood examinations showed hemoglobin 85 per cent; red blood cells 5.82 million; white blood cells 15,600 with 82 per cent polymorphonuclears. Preliminary injection with novocaine of the right sural nerve caused complete relief of symptoms; this was accordingly followed by section of the same nerve. For a few months there was complete relief of burning and pain followed, however, by identical symptoms in the other leg. She continued to complain of headache, vertigo, and pain and burning in the unoperated leg, and was observed several times in the Out-Patient Department. In 1934 a red cell count was found to be 7.60 million, and she was admitted to the hospital on March 25, 1934, for study and treatment of polycythemia.

The patient presented a plethoric appearance with deeply reddened mucous membranes and lips and dilated conjunctival blood vessels. The veins of the fundi were distended; the tongue was thick, large, and heavily coated. The heart was slightly enlarged to the left but was otherwise normal. The edge of the spleen was felt about three fingers' breadth below the left costal margin. The liver could not be felt. There were marked varicosities of both legs. In the dependent position, the left (unoperated) leg became strikingly red and seemingly filled with blood. The blood pressure was 190 systolic and 100 diastolic. The urine showed no albumin or sugar and no casts were demonstrated. The blood showed hemoglobin 116 per cent; red blood cells 7.60 million; white blood cells 14,000; polymorphonuclears 84 per cent, platelets 1,350,000.

A single venesection of 500 c.c. brought the red cell count to 6.2 million. The patient was then given phenylhydrazine hydrochloride in dosage of 0.030 gm. three times daily until the red cell count dropped to 4.50 million. One month after the be-

ginning of treatment the pains in the legs had almost entirely disappeared. She was now able to walk without difficulty and the burning sensations had gone. There was also complete relief of headaches and vertigo. Since then, the patient has been moderately well, the chief disturbing feature being the tendency to multiple thromboses of varicose veins.

B. Cases with "Cardiovascular Disease" Outstanding. In the two cases which follow, the outstanding symptoms related to the heart. Was the polycythemic state the primary condition or did it follow chronic cardiovascular disease? The incidence of marked polycythemia in adult heart disease is rare, although it may not infrequently be present in right-sided heart failure associated with disease of the pulmonary artery ("Ayerza's disease").[10] Hypertension and left ventricular failure were present in each of the two cases described below, and it seems quite unlikely that the cardiovascular disease was the cause of the polycythemia. The increased blood volume in the disease, the increased mass of circulating blood, and the marked increase in viscosity of the blood are all important factors in increasing the work of the heart and thus in leading to premature coronary disease.[11] The occurrence of multiple thromboses, both arterial and venous, in polycythemia is quite frequent and is brought out particularly in Case 4.

Case 4. Sarah S., a Russian born Jewish housewife, aged 53, came to the Out-Patient Department in July 1929 complaining of palpitation and vertigo. In 1927 she had suddenly developed severe pain in the left lower leg accompanied by bluish discoloration. At another hospital the diagnoses of hypertension, hypertensive heart disease, generalized arteriosclerosis, and possible femoral vein thrombosis were made. At the Out-Patient Department in 1929 she stated that palpitation, vertigo, and nausea had recently become so distressing that she had taken to bed. The physical examination was stated to be essentially negative except for a blood pressure of 170 systolic and 120 diastolic. The hemoglobin (Tallqvist) was 75 per cent. The diagnoses of hypertension and neurasthenia were made. In September 1931 she was admitted to the House Service where she complained of severe headache, vertigo, palpitation, precordial pain, and frequent attacks of syncope. A week before admission the left thumb had suddenly become painful, numb, and discolored. Examination at this time showed a plethoric appearance, injected conjunctivae, congested mucous membranes, and cyanotic lips. The retinal veins were distinctly widened, and there was moderate sclerosis of the retinal arteries. The heart was enlarged (apex 14.5 cm.) and a harsh systolic murmur was present at the apex. The peripheral arteries were all perceptibly thickened and tortuous, and the blood pressure was 180 systolic and 120 diastolic. Both the liver and spleen were felt two fingers' breadth below their respective costal margins. The fingers and toes were congested and cyanotic.

The urines showed traces of albumin, the sediment being negative. The blood showed: hemoglobin 145 per cent (Sahli); red blood cells 9.41; white blood cells 8,300; polymorphonuclears 79 per cent, lymphocytes 18 per cent, monocytes 1 per cent, eosinophiles 2 per cent; platelet count 2.2 million. The blood icteric index was 17.5, coagulation time 7 to 17 minutes, bleeding time 2½ minutes, fragility test 0.44 to 0.32 of NaCl solution, hematocrit 0.76, mean corpuscular volume 80 cu. micra, blood volume 6370 c.c., plasma volume 1400 c.c. The basal metabolic rate was +9 and −6 per cent, and the gastric analysis showed from 40 to 50 units of free hydrochloric acid.

Numerous venesections were performed and then phenylhydrazine was administered until the red count remained at a level of about 5.0 million per cu. mm. The patient returned to the hospital in February 1932 complaining of generalized pains

and attacks of vertigo and syncope. The hemoglobin was now 124 per cent, and the red cell count 9.15 million. Shortly after a venesection of 500 c.c. she complained of severe pain in the chest and arms. There was an extreme drop in blood pressure and serial electrocardiograms showed the changes characteristic of coronary thrombosis. Complete heart block developed. The blood non-protein nitrogen at this time was 53 mg. per 100 c.c. No further venesections were performed. Fowler's solution in large doses gave no relief.

In October 1932 she showed the signs of cardiac decompensation; blood pressure was 210 systolic and 125 diastolic; the retinal arteries were almost occluded. In December 1932 she began to have severe attacks of dyspnea. It was difficult to control the erythrocyte count which was constantly between 8 and 9.5 million. In 1933 she died at another hospital.

Case 5. Rebecca W., a 64 year old Russian-Jewish housewife, was admitted to the hospital on May 18, 1934. In 1923 she complained of vague symptoms, and hypertension was discovered. In 1926 a cholecystectomy was performed at another hospital; the red cell count was normal. In 1933 she was treated for heart disease at the same hospital; the blood pressure was 230 systolic and 140 diastolic. For 10 months she had complained of orthopnea, substernal oppression, attacks of wheezing and coughing, and occasional spells of vertigo, in one of which she was unconscious for about one-half hour. Examination in May 1934 disclosed extreme bluish redness of the face, nose, ears, lips, and tongue. Ophthalmoscopic examination showed hyperemic optic discs with blurring of the disc margins. The retinal veins were greatly dilated and the arteries extremely tortuous. Flame-shaped hemorrhages were present in each eye. Crepitant râles were present at the bases of both lungs. The heart was somewhat enlarged to the left and systolic murmurs were present over the mitral and aortic areas. Although the liver could not be felt, the edge of the spleen descended three fingers' breadth beneath the left costal margin. The fingers were greatly reddened and swollen. The peripheral arteries felt moderately thickened and tortuous. The blood pressure was 200 systolic and 125 diastolic. Laboratory findings were as follows: urine, heavy trace of albumin with occasional hyaline and granular casts; hemoglobin 170 per cent (Sahli); red blood cells 11,000,000; white blood cells 12,300; hematocrit 0.76; mean corpuscular volume 70 cu. micra; blood cholesterol 384 mg. per 100 c.c.; phthalein test 40 per cent; basal metabolic rate + 38 per cent; the electrocardiogram showed coronary changes.

A venesection of 500 c.c. was done on the sixth day. Following this procedure the patient became stuporous and could not be aroused. Right hemiplegia accompanied with Cheyne-Stokes breathing soon developed. Another venesection of 500 c.c. was done on the seventh day. The temperature rose to 105° F. and the patient expired. Autopsy showed marked generalized arteriosclerosis, cardiac hypertrophy (left), coronary sclerosis, myocardial fibrosis, bronchopneumonia, chronic vascular nephritis and congestion of the kidneys, multiple renal cysts, acute duodenal ulcer, congestion of the small intestine and liver, softening of the brain (anterior left cerebrum, two areas) and one area of hemorrhage in the right cerebellum with thrombosis of the anterior cerebral artery.

C. Cases with Symptoms Referable Chiefly to the Central Nervous System. Symptoms referable to the central nervous system are present in almost every case of the disease. In some instances, they are outstanding, and so severe as to make the consideration of brain tumor a serious one.[12] Although in none of our cases were the symptoms of this degree of severity, an examination of the records of another hospital showed that in a number of cases, brain tumor was at first suspected, although the final diagnosis was

polycythemia vera. Occasionally, the differential diagnosis between the two conditions is extremely difficult since both polycythemia and intracranial neoplasm may result in lethargy, headache, vertigo, scotomata, blurring of vision, congestion of the retinal vessels and papilledema. Colored scotomata were commonly present, particularly when the red cell count was above 8.0 million.

Case 6. Jacob G., a 65 year old Russian-Jewish unemployed inmate of a home for the aged, began to have severe headaches in 1927. In 1931, he developed right hemiplegia and was confined to another hospital where the diagnosis of hypertension was made. In October 1932, when he came to the Out-Patient Department of this hospital, he complained chiefly of severe headache, vertigo, tinnitus, and colored scotomata, together with increasing nervousness, insomnia, and weakness. Other symptoms were dyspnea, slight precordial pain, palpitation, constipation, and paresthesias of the hands and feet. Examination at this time disclosed a plethoric appearing man. The heart was somewhat enlarged, the aortic second sound accentuated, and a rough systolic murmur was heard over the entire precordium, principally over the aortic region. The blood pressure was 190 systolic and 90 diastolic, and the peripheral arteries were greatly sclerosed. The laboratory data were as follows: hemoglobin 124 per cent; red blood cells 8.96 million; white blood cells 12,400; polymorphonuclears 84 per cent; platelets 1.24 million. With reduction of hemoglobin concentration and red cell count to approximately normal figures, there was complete subsidence of all the symptoms. These recurred with relapse to polycythemic levels and were again relieved by multiple venesections.

Case 7. Robert S., a 39 year old Russian-Jewish storage battery worker, was referred to the Out-Patient Department in February 1937 by his family physician who had made the presumptive diagnosis of polycythemia. The patient had noticed increasing sluggishness in the past year, and readily fell asleep at times during the day. He found it hard to concentrate on simple problems and had noticed a rather marked change in his disposition so that he became readily angered. In the past month he had developed frequent spells of dizziness and was often nauseated. On one occasion, he vomited. For a month also he had noticed frequency of urination and nocturia 5 to 6 times. Physical examination showed a very plethoric-appearing man with extremely red face, hands, and feet and congested, somewhat bluish mucous membranes. The retinal veins were greatly congested and the reflexes were hyperactive. *Neither the spleen nor liver was felt.* Involuntary twitchings of the muscles of the arms and legs were noted at times. At another visit, the spleen was just palpable. The blood pressure was 136 systolic and 90 diastolic. The laboratory data were as follows: hemoglobin 150 per cent (Sahli); red blood cells 8.0 to 8.7 million; white blood cells 12,000; hematocrit 74 to 80 per cent; platelet count 400,000 to 800,000; blood viscosity 13.4 (normal 4–5). The urine showed a trace of albumin, the sediment was negative. With the induction of an iron-deficiency regime, there was complete symptomatic relief.

Case 8. Gussie F., a 49 year old Austrian-Jewish housewife, was admitted to the hospital in October 1933. In 1905 she was treated for chlorosis at another hospital. Beginning in 1931, at about the time of menopause, she complained of severe hot flashes, headache, vertigo, and tinnitus. In 1932, following extraction of a tooth, she bled profusely for 36 hours; hemorrhage was finally controlled by packing. The headache and spells of vertigo became worse and were at times associated with momentary loss of memory. In 1933 she developed involuntary twitching of the fingers which would cease when attention was directed to this peculiar motion. For two years, she had visited several physicians and a variety of diagnoses had been made: menopause, neurasthenia, cerebral arteriosclerosis. Three months before admission,

she was constantly flushed and red; her lips became extremely full and dry so that she was constantly either biting or licking them. She became increasingly dyspneic and complained of palpitation and fatigue. She lost her appetite, developed severe epigastric distress and constipation and had nocturia. Two weeks before entry, she had a severe spell of vertigo lasting several hours and associated with complete amnesia. She was finally seen by a physician who, noticing her plethoric appearance, did an erythrocyte count, found it elevated, and made a tentative diagnosis of polycythemia. She was referred to the hospital on October 4, 1933, for observation and therapy. Physical examination revealed an extremely red face. The conjunctivae were deeply injected and the venules over the cheeks greatly dilated. The lips were purplish in color, the gums intensely red, the tongue large, "beefy," and deeply fissured. The retinal veins were extremely dilated. The lungs were normal. The heart showed no enlargement. A rough systolic murmur was present over the apical region. The liver and spleen were both felt three fingers' breadth below their respective costal margins. The reflexes were hyperactive but otherwise normal. A "Parkinsonian" type of tremor of the fingers was present and there was also constant licking and biting of the lips. A neurologist suggested involvement of the basal ganglia.

The laboratory data were as follows: urine, trace of albumin, no casts; blood: hemoglobin (Sahli) 118 per cent; red blood cells 10.2 million; white blood cells 10,800; platelets 2,500,000 per cu. mm.; differential count of the leukocytes: polymorphonuclears 81 per cent, lymphocytes 14 per cent, monocytes 3 per cent; eosinophiles 1 per cent, basophiles 1 per cent. Blood non-protein nitrogen was 41 mg. per cent. Basal metabolic rate was + 5 per cent. In the second week of the patient's stay, thrombophlebitis of the veins on the inner aspect of the left thigh developed. Several venesections were performed and Fowler's solution administered, although this was later discontinued. On phenylhydrazine hydrochloride and more recently on an iron deficient regime there has been complete disappearance of all her symptoms.

D. Cases with Gastrointestinal Symptoms Outstanding. In common with the remainder of the body, the gastrointestinal tract shares in the general plethoric condition. Congestion in the various abdominal organs produces various types of symptoms referable to the liver, spleen, stomach, or intestines. Constant pain, apparently due to hepatic congestion, was present in Cases 11 and 12. In the first of these cases, the right-sided pain led to a diagnosis of appendicitis and the patient was operated upon; in the second case, the diagnosis of gall bladder disease was for some time entertained. Many of the patients complain of pain or a heavy sensation in the region of the spleen (Case 10). The co-existence of peptic ulcer with polycythemia has been commented upon by several observers.[13] In our series, peptic ulcer was found in four cases and suspected in another case. At times, the symptoms of the ulcer dominate the picture, as in Cases 9 and 13.

Case 9. Samuel W., a 63 year old Russian-Jewish storekeeper, was admitted on August 11, 1930, complaining of generalized abdominal cramps of four days' duration, together with vomiting and obstipation for 1 day. Prior to this illness, he had considered himself in good health. Examination showed a decidedly plethoric appearance, emphysematous lungs, greatly thickened brachial and radial arteries, blood pressure 140 systolic and 88 diastolic, and abdominal distention with spasm in the region of the umbilicus. Blood examination showed hemoglobin 130 per cent (Sahli); red blood cells 8.8 to 9.95 million; white blood cells at first 20,600, later 9,100; platelets 594,000. The urine showed a very slight to slight trace of albumin. A gastro-

intestinal series showed duodenal ulcer. The sharp attacks of abdominal pain continued and finally led to a laparotomy on September 25, 1930, at which time a perforating duodenal ulcer with peritonitis was found. A posterior gastro-enterostomy was performed, following which the patient developed massive collapse of a lung and died three days after operation. Autopsy revealed the presence of four deep, punched-out ulcers of the duodenum, adhesive peritonitis, bronchopneumonia, possible luetic aortitis, and considerable congestion of all the abdominal viscera.

Case 10. Frank R., a 58 year old Russian Jewish storekeeper, was admitted to the hospital on August 13, 1931, complaining of a "lump" in the left upper part of the abdomen. Although he had complained of this symptom for several years a definite diagnosis had not been made. During the eight months before admission, the lump in the left upper abdomen had grown noticeably larger and during that time he complained of a feeling of epigastric fullness after meals, constipation, gastric distress, profuse sweating, moderate itching of the skin, and slight dysuria. In the past, he had bled severely from the "tonsils" (cause unknown); from the rectum, necessitating at that time hospitalization; and from the gums upon extraction of teeth. Headaches had been present for years. Examination revealed an extremely ruddy color of the skin, and deeply congested buccal mucous membranes and pharynx. The lungs showed increased resonance (interpreted as emphysema). The heart showed moderate hypertrophy. The spleen was greatly enlarged, being palpated below the umbilical line. The liver edge was not felt. The hands, fingers, and fingernails were very florid and ruddy. The hematological findings were as follows: hemoglobin 124 per cent; red blood cells 7.36 million; white blood cells 21,300; polymorphonuclear cells 81 per cent; platelets 1.14 million; bleeding time 3 minutes; coagulation time 7 minutes. The basal metabolic rate was + 50 per cent. The urine showed a very slight trace to a trace of albumin.

Since the teeth were found to be extremely carious, extraction was thought advisable. Severe hemorrhage took place when a few teeth were extracted. The red cell count dropped to 4.45 million and the hemoglobin to 86 per cent (Sahli), the leukocyte count rising to 48,000. Ten teeth were extracted during three sittings, and on each occasion bleeding was profuse, requiring packing and pressure. Six days after the last extraction, the patient felt better and was discharged home.

Case 11. Sarah M., a 26 year old Russian-Jewish saleswoman, was admitted to the private service (surgical) of the hospital on June 13, 1932, because of recurrent pain in the right side of the abdomen. Examination showed flushing of the face and slight tenderness in the right lower quadrant. The urine was negative, the leukocyte count 14,600. Operation was performed and disclosed a hyperemic edematous appendix and a congested corpus luteum cyst of the left ovary. Appendectomy and resection of the left ovary were performed. A large hematoma of the operative wound developed with much oozing of blood into the incision. The red cell counts at this time were found to vary from 5.3 to 7.3 million, and the hemoglobin was 113 per cent (Sahli). The diagnosis of polycythemia vera was indicated. Pain in the abdomen identical to that prior to operation persisted. Almost a year later (April 1933), a roentgenologist discovered splenomegaly in the course of a gastrointestinal series. Shortly after, the following additional history was obtained. The patient had considered herself well until 1929 when she began to have severe headaches associated with scotomata, nausea, and vomiting. These were considered to be migraine, and indeed her mother had had identical headaches for many years. In 1930 a tooth was extracted; this was followed by extreme hemorrhage, finally necessitating packing. About this time she noticed persistent "redness" of the eyes; an oculist found nothing abnormal. In 1931 she noticed that her hands were red, blotchy, and cold, and apparently swollen. Her feet were also noticeably red, and frequently pained her in walking. The headaches became worse and were often associated with spells of vertigo and paresthesias of the hands, face, and tongue. A nose-and-throat spe-

cialist failed to find any abnormal sinus condition. In the early part of 1932 she began to have attacks of pain in the right side of the abdomen; these usually began in the upper quadrant and radiated downwards. At times they were associated with the severe attacks of headache and vomiting. Soon the pain became almost constant. In one bout of severe abdominal pain associated with vomiting, a physician made the diagnosis of acute appendicitis and she was operated upon, as noted above. The pain had continued and had even grown worse.

On examination in 1933 there was intense redness of the face and neck. The conjunctival blood vessels were greatly injected. The fundal veins were greatly dilated. The mucous membranes of the lips, mouth, and throat were brilliantly red. The tongue was large and well coated. The lungs and heart showed no abnormalities. The edge of the liver was felt three fingers' breadth below the right costal margin and was extremely tender. A hard spleen was felt in the comparable position on the left. The hands and feet were reddish blue, blotchy, and cold to the touch. The dorsalis pedis arteries were readily palpable. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. The laboratory data were as follows: urine—no albumin, sugar, or casts; blood—hemoglobin 124 per cent (Sahli); red blood cells 7.24 million, white blood cells 9,800; differential count of the white cells: polymorphonuclears 78 per cent (21.5 per cent immature forms); lymphocytes 11.5 per cent; monocytes 2.5 per cent; eosinophiles 3.0 per cent; basophiles 5.0 per cent. Platelet count was 1,500,000 per cu. mm.

There was satisfactory response to phenylhydrazine therapy with resultant diminution, and at times cessation, of all of the above symptoms. The abdominal pain disappeared after the erythrocyte count had remained at a level of about 5.0 million for several months.

Case 12. Charles B., a 52 year old Russian-born Jewish merchant, was first seen in January 1935. In 1933 he began to complain of a sense of pressure in the right upper quadrant. Since this was accompanied with belching and heart burn and failure of the gall bladder to visualize with the Graham test, the diagnosis of gall bladder disease was made by his family physician and treatment with a fat-free diet instituted. When sense of pressure recurred later, he was studied at another hospital where a mass in the left upper quadrant was discovered. It was thought this might be due to an enlarged kidney, and two cystoscopic examinations were accordingly done without a definite diagnosis being made. The sense of pressure in the right upper quadrant continued, and he consulted various physicians without relief. In December 1934, while in bed, he was suddenly seized with severe pain and a vise-like sensation in the mid-chest radiating down the left arm and associated with severe dyspnea. This attack lasted for seven hours. He was in bed for two weeks. At the end of that period, routine blood counts showed hemoglobin 140 per cent (Sahli) and red cell count of 6.80 million. Additional history in June 1935 was obtained of the following: frequent very severe headaches for about four years, coming in attacks, lasting two to three days at a time, associated with blurring of vision and at times with much belching of gas and nausea. Vertigo was occasionally present. The eyes had felt "heavy" for about six months. For about a year he had noticed paresthesias of the thumb and index finger of the left hand and, for three months a peculiar creepy sensation down both arms. His hands had been as "red as a beet" for about 15 to 20 years, especially so in the summer time.

Examination disclosed the following: a plethoric appearance; congested conjunctivae; widely dilated fundal veins with normal appearing arteries; slight red cyanosis of the lips and mucous membranes; a heavily coated, normal sized tongue; a tender liver edge felt three fingers' breadth below the right costal margin and a firm spleen three fingers' breadth below the left costal margin. The heart was slightly enlarged to the left. The blood pressure was 116 systolic and 70 diastolic. There was a dusky coloration of the finger tips. The urine showed no albumin, sugar, or

casts. The blood showed: hemoglobin 128 per cent (Sahli); red blood cells 7.69 million; white blood cells 12,600; differential count: polymorphonuclears 93 per cent, lymphocytes 5 per cent, monocytes 1 per cent, eosinophiles 1 per cent; blood platelets 898,000.

The patient was given phenylhydrazine hydrochloride in dosage of 150 mg. daily with resultant diminution in erythrocyte count. When the erythrocyte count had remained in the vicinity of 5.0 million per cu. mm. for about a month, the sense of fullness in the right upper quadrant and most of the digestive disturbances disappeared. There was complete cessation of the violent headaches and visual disturbances which had been prominent before. The cardiac condition gradually improved so that the patient could continue at his business.

Case 13. Max C., a 44 year old Russian-Jewish laborer, came to the Out-Patient Department complaining of pain in the left upper quadrant, just to the left of the epigastrium, appearing ¾ hr. after a meal, lasting for about 30 minutes or more, and relieved immediately by taking food. For several years he had been constipated and had complained of "gas" and sour eructations. Other symptoms were headache, frequent spells of dizziness, and colored scotomata. Physical examination showed a very plethoric appearing man, with dilatation of the superficial blood vessels of the skin of the face, the conjunctivae, and buccal mucous membranes. Small nevi of the face were present. The tongue was small, shiny, and well coated. The edge of the liver was felt one finger's breadth below the right costal margin, the splenic edge just felt. The laboratory data were as follows: hemoglobin 138 per cent (Sahli); red blood cells 8.75 million; white blood cells 18,400; polymorphonuclears 87 per cent; lymphocytes 8 per cent; monocytes 2 per cent; eosinophiles 1 per cent; basophiles 2 per cent; platelets 1.74 million; platelet volume 2 per cent; hematocrit 76 per cent. Gastric analysis—a maximum of 16 units of free HCl. Blood volume 8,900 c.c. Basal metabolic rate + 10 per cent. The gastrointestinal series showed a slight irregularity at the lesser curvature of the duodenal cap, interpreted as a small duodenal ulcer. On a modified Sippy régime and multiple venesections, the patient's symptoms completely disappeared and the blood picture became normal.

E. Cases with "Arthritis" Outstanding. In some cases of polycythemia pains in the joints and limitation in motion make the diagnosis of chronic arthritis a definite possibility. This was the situation in two of our cases.

Case 14. Gertrude M., a Russian-born Jewish housewife, aged 50, came to the Out-Patient Department on June 4, 1936, complaining of vague joint pains of two years' duration. For six months, the pains had become more severe and were present in the lower back, the shoulders, knees, elbows, wrists, and finger joints. For two weeks, numbness and tingling of the fingers had been present. The diagnosis of chronic arthritis had been made by her local physician. Examination at the patient's first visit failed to reveal any abnormalities except possibly an enlarged spleen, and a definite diagnosis could not be made. A sedimentation rate was requested. Because this was found to be unusually slow, the possibility of polycythemia was considered. Hematocrit and erythrocyte determinations were respectively 0.62 and 6.16 million per cu. mm. On June 11, a large spleen and liver were discovered and the tentative diagnosis of polycythemia made. The patient was then referred to the Blood Clinic where physical examination disclosed a plethoric-appearing woman with congested conjunctival blood vessels, a large well-coated tongue, hepato- and splenomegaly (liver and spleen each two fingers' breadth below their respective costal margins), an essentially normal heart, and blood pressure of 170 systolic and 110 diastolic. The legs and feet showed no abnormalities. The blood showed the following: hemoglobin 102 per cent (Sahli); red blood cells 6.35 to 7.28 million; hematocrit 0.62;

white blood cells 19,700; platelets 870,000 to 3.0 million. Because of the high platelet count and the consequent possibility of thrombosis, it was thought inadvisable to use phenylhydrazine, and the patient was therefore given a course of spray roentgen-ray therapy with resultant amelioration in symptoms and slight drop in red cell count. She failed to return for further observation.

Case 15. Mabel F., a Russian-Jewish housewife, was referred to one of us on March 13, 1937, the diagnosis of polycythemia already having been established at another hospital. In January 1937, she began to have numbness of the legs accompanied by pain in the back and pain radiating from the thighs to the ankles. Soon the legs, particularly the left one, became stiff, and she required assistance in getting into and out of bed. Finally, she developed constant "grinding" pain in both legs and found it difficult to walk about. She was told she had arthritis. In February 1937 she noticed a heavy sensation in the left upper abdomen and felt a large "lump." She was admitted to another hospital for study where the "lump" was discovered to be a very large spleen, and an erythrocyte count of 8.0 million was found. Few other symptoms were present except that she had noticed "sluggishness" for about a year and anorexia and "gas" for a few months. The past history was negative except that two years previously, following a dental extraction, she had bled for 18 hours, requiring packing of the tooth socket.

Examination on March 13 and at subsequent occasions when the patient was admitted to the hospital disclosed a plethoric-appearing woman, with slight cyanosis and marked flushing of the mucous membranes and conjunctivae. The retinal veins were greatly distended. The tongue was reddened. Examination of the chest, heart, and lungs was entirely negative. The liver edge was felt three to four fingers' breadth below the right costal margin; the spleen was extremely large, occupying the entire left upper quadrant. The blood pressure was 130 systolic and 90 diastolic. There was slight to moderate limitation in motion of the knee joints and the patient presented a somewhat spastic gait. The knee-jerks were hyperactive; the vibration sensation was normal. The disturbance in gait seemed out of all proportion to the physical findings. An orthopedist felt she had somewhat pronated feet and tight heel cords. Further observation pointed to a diagnosis of hysteria, at least as an associated phenomenon. The laboratory data were as follows: hemoglobin 123 per cent; red blood cells 8.63; white blood cells 10,800; polymorphonuclears 82 per cent (26 band forms), lymphocytes 6 per cent, monocytes 5 per cent, eosinophiles 5 per cent; basophiles 2 per cent. One nucleated red blood cell was seen. Platelets were 362,000; hematocrit 66 per cent. Basal metabolic rate + 2 per cent; gastric analysis —a maximum of 5 units of free HCl after an alcohol test meal; urines—albumin very slight trace on one of three occasions; sediment negative; non-protein nitrogen 39 and 31 mg.; uric acid 4.9 and 4.8 mg.

After the above studies were completed, the patient was venesected and placed on an iron deficiency diet. There was rapid subsidence of the symptoms referable to the legs, and within three months there was neither pain nor limitation in motion. The patient has remained well on an iron deficiency regimen without further treatment.

F. Cases with "Nephritis" Outstanding. Polycythemia may be confused with chronic vascular nephritis. A plethoric appearance may be common to both conditions. Furthermore, most cases of polycythemia in our series have shown hypertension, slight degrees of albuminuria, at times a few casts, and at times a definite although slight elevation in the blood non-protein nitrogen (table 3). In one of our cases, the diagnosis of severe nephritis seemed quite definite; when polycythemia was later discovered, the patient had an excellent therapeutic response following the institution of an iron-deficiency regimen.

Case 16. Rebecca G., a Russian-born Jewish housewife, aged 70 years, was admitted on June 17, 1936, in a state of mental confusion. She had been followed in the Out-Patient Department since August 1935. At that time she complained of severe headache of one year's duration, spells of weakness with a sensation of faintness in the past month, and a shooting pain in the left thigh a week previously, necessitating admission to the Emergency Ward. At this time albuminuria was discovered together with the presence of granular casts. The white blood cell count was 15,000. She had frequency of urination together with nocturia, 4 to 5 times. On examination the heart was found slightly enlarged, the blood pressure 200 systolic and 100 diastolic, the abdomen negative, and the urine showed a slight trace of albumin with a rare red blood cell and a rare hyaline cast. The blood non-protein nitrogen was 47 mg. per 100 c.c. The diagnoses of hypertension and chronic vascular nephritis were made and the patient placed on a low protein diet. In a few days, on account of recurrence of pain in the left leg, she was referred to the Orthopedic Clinic where no evidence of arthritis or sacroiliac disease was discovered. She was lost from ob-

TABLE III

Laboratory Data

Case	Hgb. (Sahli) %	R.B.C. (Millions)	W.B.C.	Platelets (Millions)	Hematocrit %	Polymorphs %	Blood Viscosity (Units)	Albuminuria	N.P.N. (mg. %)	Blood Volume (Total c.c.)	B.M.R.	Gastric Analysis (Units of Free HCl)
1	120	7.61	14,100	.789	—	76	—	VST-ST	41	—	—	—
2	115	7.00	18,900	2.850	58	80		Neg.	42	10,100	+5 +0	—
3	116	7.60	14,000	1.350	—	84		Neg.	—	—	—	—
4	145	9.41	8,300	2.200	76	79		SPT-ST	42	6,370	+9 −6	40–50
5	170	11.00	12,300	—	76	80	—	LT	53	—	+38	
6	124	8.96	12,400	1.240	68	84	—	T	32	—	+15 +11	—
7	150	8.70	12,000	.800	74–80	82	13.4	VST	—	6,700	−15	
8	118	10.20	10,800	2.500		81	—	SPT	41	—	+ 5	—
9	130	9.95		.594	—	87	—	SPT-LT	44	—	—	—
10	124	7.36	21,300	1.140	—	81	—	VST-T	47	—	+50	—
11	124	7.24	9,800	1.500	—	78	—	Neg.	—			
12	128	7.69	12,600	.898	64	93		Neg.	—			
13	138	8.75	18,400	1.740	76	87	15–17	Neg.	—	8,900	+15	18
14	102	7.28	19,700	.870 to 3.000	62	75	—	Neg.	—		—	—
15	123	8.63	10,800	.362	66	82	10.0	O-VST	39	7,740	+ 2	5
16	140	9.70	15,400	.750	70	92	—	VST-T	56	—	—	—
17	150	8.27	13,500	1.200	67	84	—	ST-T	37–40		+13	
18	104	9.00	18,000	1.000 +	65	85	—	SPT-VST	30	—	+21	—
19	120	9.00	20,000	1.500	79	86		ST	35–41	12,000–15,000	+35	
20	161	9.10	9,500	.660	82	78	14.0	VST	65	17,500	+23	

servation until a second admission to the hospital on July 17, 1936. At that time, the following additional history was obtained: dimness of vision for about three years; hypertension and headaches for about two years associated with increasing weakness; an attack of extreme dyspnea occurring six weeks previously for which she had been admitted to another hospital and discharged in four days; extreme weakness for four weeks; headache, vertigo, tinnitus, impaired memory, and increasing mental confusion for about two weeks; vomiting on the day of entry.

Examination disclosed a red-faced, restless old woman who was obviously much confused. The skin and mucous membranes presented a dusky purplish coloration, and several small telangiectasiae were present on the face. There was bilateral arcus senilis and cataract formation. The conjunctivae were greatly injected. The tongue was thick, dry, and thickly coated. The heart was slightly enlarged to the left. The aortic second sound was somewhat accentuated. There was an occasional ventricular extrasystole. The peripheral arteries were thickened and tortuous. Blood pressure was 208 mm. of mercury systolic and 120 diastolic. The lungs showed a few râles at both bases. The liver edge was felt two fingers' breadth below the right

costal margin, and the spleen, which was thin and rather deep, was felt with some difficulty two fingers' breadth below the left costal margin. There was moderate clubbing of the fingers.

The urine showed a very slight trace to a trace of albumin; no casts were present at this time; specific gravity varied between 1.010 and 1.020. The blood examination showed the following: hemoglobin 140 per cent (Sahli); red blood cells 10.0 million; white blood cells 15,400. Further blood studies confirmed these findings: hemoglobin was between 130 and 145 per cent (Sahli); red blood cells between 8.7 and 9.7 million; platelets 750,000; reticulocytes 2.5 per cent; hematocrit 70 per cent. Frequent venesections were performed with striking benefit to the mental state and finally with complete relief of all the other symptoms.

G. Cases with a Multiplicity of Symptoms Suggesting Neurasthenia. The diagnosis of neurasthenia may either be made by exclusion or in a more positive fashion when a host of seemingly unrelated symptoms is present. In the case to be described the great multiplicity of symptoms suggested neurasthenia. The possibility is naturally present that both the "organic" disease polycythemia and the functional disorder "neurasthenia" were present together. However, the complete relief of all the symptoms when the blood was brought to a normal level, the return of identical symptoms with relapse to the polycythemic state, and again relief with appropriate therapy point to polycythemia as being the definite cause of the numerous symptoms.

Case 17. Flora S., a 55 year old Russian-Jewish housewife, first came to the Out-Patient Department in 1932. In 1924 she began to complain of frequency of urination, nocturia, vertigo, spots before the eyes, ease of fatigue, "pressing" feelings in the arms, thighs, chest, and rectum together with numbness and tingling of the fingers. A doctor told her she was suffering from "change of life" and high blood pressure (blood pressure 215). In June 1932 at the Out-Patient Department she presented a flushed face, a large "geographic" tongue, a slightly hypertrophied heart with a soft systolic murmur, and a blood pressure of 182/108. Several urine specimens showed the presence of traces of albumin and occasional hyaline and granular casts. The diagnoses of hypertension, early hypertensive heart disease, and neurasthenia were made; nephritis was considered because of the urinary findings.

From June 1932 to October 1933, the patient was treated symptomatically in the Out-Patient Department, especial emphasis being laid on the neurasthenic state and hypertension. In October 1933 a physician suspected the possibility of polycythemia on account of the patient's plethoric appearance. The blood showed hemoglobin (Tallqvist) 85 per cent; red blood cells 7.89 million; white blood cells 23,000. The diagnosis of polycythemia was then made. Further studies demonstrated a warm, moist skin, congested conjunctival blood vessels, greatly reddened mucous membranes, large red tongue, cardiac enlargement, hepato- and splenomegaly, and large red hands and feet. The laboratory findings were: hemoglobin 150 per cent (Sahli); red blood cells 8.27 million; white blood cells 13,500; hematocrit 0.67; bilirubin 0.97 mg./100 c.c.; basal metabolic rate + 13 per cent. With control of the patient's hemoglobin and red cell counts first by phenylhydrazine, and more recently by an iron-deficiency regimen, the patient has lost all of her numerous symptoms and feels entirely well.

H. Cases with Symptoms Referable to Several Systems or Difficult to Classify. As already brought out, most cases of polycythemia present a multiplicity of symptoms, although emphasis is usually placed upon one or

another bodily system. In a few cases the complaints are referable to most of the systems without any single one being especially selected.

Case 18. Myer A., a 60 year old Russian-Jewish cantor, first entered the hospital on June 29, 1929. In 1924 he had been studied at another hospital where the diagnosis of polycythemia had been made and the following history obtained: easy fatigue for three years, increasing weakness for eight months, increasing dyspnea for about two months, gastric distress, and severe pains in the legs. Examination at that time showed bluish-red cyanosis of the face, injected conjunctivae, engorged fundal veins, deeply red mucous membranes, cardiac enlargement with a systolic murmur, splenomegaly (three fingers' breadth), and clubbed fingers. The blood pressure was 150 systolic, 80 diastolic. Hemoglobin was 170 per cent; red blood cells 10.7 million; white blood cells 10,500; platelets 350,000. Basal metabolic rate was +33 per cent. The urine showed a slight trace of albumin. After two venesections and one short course of benzol therapy, the patient was discharged from the hospital. In 1926 he was troubled chiefly with severe upper abdominal pain and on one occasion went into collapse. He was later found to have a gastric ulcer which had perforated into the lesser omental sac. In 1927 and 1928 he was troubled chiefly with dyspnea, weakness, and pains in the legs. Auricular fibrillation developed, and he was thought to have coronary thrombosis. The blood pressure was 150 systolic and 90 diastolic. The hemoglobin was between 150 and 165 per cent; red blood cells between 6 and 10 million. Courses of phenylhydrazine and roentgen-ray therapy were given without definite relief.

At the Beth Israel Hospital in 1929, he complained of headache, poor vision, increasing deafness, extreme weakness, marked dyspnea, anorexia, constant right upper quadrant pain, and severe pains in the legs chiefly at night. Examination showed a very red, roughened tongue, irregular reddened spots on the soft palate, auricular fibrillation, and a large liver and spleen. The hemoglobin was 104 per cent (Sahli); red blood cells 9.0 million; white blood cells 18,000; polymorphonuclear cells 85 per cent; blood platelets more than a million per cu. mm.; hematocrit 65 per cent. The urine showed a very slight trace of albumin. A sternal bone-marrow biopsy showed extreme hyperplasia, particularly of the erythro-normoblastic series. While in the ward, he complained chiefly of cramplike pains in the legs mostly nocturnal, unrelieved by heat and rest, and relieved somewhat by walking. In 1930 the pains in the legs dominated the clinical picture. The dorsalis pedis and posterior tibial arteries were readily felt, although they showed evidence of much sclerosis. Treatment for the polycythemia with occasional venesections, phenylhydrazine, etc. was uniformly unsatisfactory.

In 1931, 1932, and 1933, frank congestive failure was present. By 1934 the liver and spleen had become greatly enlarged, occupying almost the entire abdomen. At this time he showed definite anemia: the red cell count was 3.15 million, hemoglobin 80 per cent (Sahli). The leukocyte count was normal, the platelets 1.50 million. The stained smear showed 10 per cent myelocytes, and there was marked variation in size and shape of the red cells. Shortly thereafter the patient died.

Case 19. Hyman A., a Russian-Jewish tailor, aged 45, first came to the Out-Patient Department in 1929 complaining of a lesion of the upper lip of four years' duration. The diagnosis of sycosis ("barber's itch") was made and many methods of therapy were tried without relief. In May 1932 the patient appeared in the Medical Clinic complaining of severe frontal headache of two months' duration, epigastric distress, and constipation. On examination it was noted that the face was flushed and slightly cyanotic and that the mucous membranes and conjunctivae were injected. The radial arteries appeared to be unusually hard and tortuous. The blood pressure was 148 systolic and 100 diastolic. The clinical diagnoses of chronic constipation and premature arteriosclerosis were made. The patient continued to complain, and

chiefly because of the red color of the face a blood examination was made which showed the following: hemoglobin 100 per cent (Tallqvist); red blood cells 7.97 million; white blood cells 14,700; polymorphonuclear cells 85.5 per cent; platelets 815,000. The diagnosis of polycythemia vera was made at this time. Several teeth were extracted with the resultant loss of a great deal of blood. The patient was not seen for one year thereafter. In the Dental Clinic in 1933 he was found to show striking congestion of the mucous membranes without any apparent inflammation, and again the diagnosis of polycythemia was made. At that time, the hemoglobin was 108 per cent (Sahli) and red blood cells 9.18 million. The basal metabolic rate was + 23 per cent. Again the patient was lost from observation until 1935 when he was found in the Skin Clinic receiving injections of manganese for the still present sycosis. Severe pain had developed in the left buttock at the site of several of the injections. The pain became so severe as to necessitate admission to the House.

At this time (September 2, 1935), the history was obtained of headache for 10 years, vertigo 4 years, and a multiplicity of symptoms for 2 years. These were lassitude, insomnia, weakness, fullness in the head, loss of memory, dimness of vision, tinnitus, occasional attacks of epistaxis, dyspnea, and palpitation on exertion, occasional substernal oppression, easy fatigability, a sense of fullness in the stomach, frequent nausea with occasional spells of vomiting, epigastric pain, pain in the left upper quadrant, and severe constipation. In August 1934 transient right-sided paralysis of the face, right arm, and right leg had occurred. Also present were numbness and tingling of the extremities and increasing deafness.

Examination on September 2, 1935, showed a little man with extreme ruddy cyanosis (he appeared to be in a constant blush), especially noticeable over the cheeks, the tip of the nose, and the ears. The mucous membranes were deeply cyanosed. Over the left upper lip there was a raised, purple area measuring 2 by 0.5 cm. Ophthalmoscopic examination showed a deeply colored retina with striking engorgement of the retinal veins and marked tortuosity of the vessels. The tongue was very large, beefy red, and thickly coated. Engorged superficial veins were present over the scalp and neck. No abnormalities of the heart or lungs were noted. There was marked dilatation of the superficial abdominal veins. The edge of the liver was felt two fingers' breadth below the right costal margin, and the spleen was felt in a similar position on the left. The finger tips were greatly cyanosed and there was slight thickening of the terminal phalanges. The toes showed striking cyanosis and the nails were greatly thickened. The peripheral arteries of the feet and legs were readily palpable. Over the left buttock there was a swelling the size of a small orange, very tender to touch.

The laboratory findings were now as follows: hemoglobin between 110 and 130 per cent; red blood cells 8 to 10 million; white blood cells 13,000 to 30,000; hematocrit 0.77 to 0.79; platelets 1,630,000 to 2,050,000 with a platelet volume of 1.5 per cent. The total blood volume was 12,000 to 15,000 c.c. The capillaries of the nail bed showed marked dilatation, and great tortuosity with many "figures of eight." The urine showed a slight trace of albumin. The basal metabolic rate was + 35 per cent, bilirubin 1.92 mg./100 c.c. Needle aspiration of the swollen buttock showed old blood. At operation a large hematoma was discovered, the source of blood being an artery of moderate size which was partially covered by friable thrombus. This was ligated. Subsequently, the patient was venesected a number of times and placed on an iron-deficient diet with complete relief of symptoms. In 1936, however, he complained of distress and nausea occurring one-half to one hour after meals. Roentgen-rays of the gastrointestinal tract revealed slight irregularity of the lesser curvature aspect of the duodenum suggesting either ulcer or periduodenal adhesions. The symptoms were quickly relieved by a bland diet.

Case 20. Samuel C., a 62 year old Russian-born Jewish shoemaker, was referred to one of us in May 1937 for diagnosis of possible polycythemia. Six years

previously prostatectomy had been performed for hypertrophied prostate. Two years before he had noticed an increasing redness of the face and head and particularly of the nose; during the summer, his skin felt unusually warm and its redness always excited comment. For about a year he had felt a throbbing sensation in the head almost constantly and two months ago had noticed reddish nodules of the eyelids with a troublesome burning sensation. He was referred to a dermatologist for a possible skin condition, and the diagnosis of polycythemia was indicated. Examination revealed a small man with extreme reddish cyanosis of the lips and mucous membranes and an almost startling redness of the face and particularly of the nose. Many small nevi were present. The conjunctivae showed striking congestion with the presence of two pea-sized subconjunctival nodules, one in each eye. The retinal veins were greatly distended, the arteries being narrowed and tortuous with "silver-wire" effects. The tongue was large with a normal coat. The chest showed some increase in anteroposterior diameter. The heart was not enlarged and showed no abnormal findings. The blood pressure was 165 systolic and 110 diastolic. The liver was not felt, but the edge of the spleen was felt one finger's breadth below the left costal margin. There was marked sclerosis of the peripheral arteries. The laboratory data were as follows: hemoglobin 161 per cent; red blood cells 9.10 million; white blood cells 9,500; platelets 660,000; hematocrit 81 to 82 per cent; total blood volume 17,500 c.c. with plasma volume 3320 c.c.; urine, very slight trace albumin in all specimens, sediments negative; non-protein nitrogen 65 mg.; creatinine 2.2 mg.; basal metabolic rate +23 per cent.

The patient required a large series of venesections and was then placed on an iron-deficiency diet. There was remarkable subsidence in the redness of the skin and in the conjunctival congestion, although the nodules were still present. When the hemoglobin and erythrocyte count had reached normal levels, the blood pressure became diminished to 126 systolic and 70 diastolic, the urine failed to show albumin, and the blood non-protein nitrogen was reduced to 40 mg./100 c.c. The chronic conjunctivitis finally subsided entirely.

Analysis of Cases

Symptoms. An analysis of the symptoms encountered in this series of cases is presented in table 1. Neuropsychiatric symptoms predominated. Headache, usually quite severe, was present in 17 of the 20 cases; in 3 cases, typical attacks of migraine had been present for years. Vertigo was complained of in 14 cases. Various types of visual disturbances, particularly spots before the eyes, were frequently encountered, and in 6 cases colored scotomata were present. Paresthesias of the extremities—numbness and tingling—were present in 12 cases. Weakness, so common to many conditions, was complained of in 8 cases. Next in frequency to the neurological symptoms were those referable to the abdomen or the gastrointestinal tract. Thus abdominal pain was complained of in 10 cases; constipation was present in all but 6 cases. In 4 cases a peptic ulcer was found and in a fifth case suspected. Cardiovascular symptoms were common: thus dyspnea, palpitation, precordial pain, etc. were present in 8 cases; circulatory disturbances of the legs, feet, or hands were present in 6 cases; and various types of thromboses (cerebral, coronary, venous, arterial) were present in 9 cases. The symptoms referable to the extremities were among the most interesting. Several patients stated that their hands had always been red, warm, and moist, and tended to become swollen in hot weather. Two patients had the

typical symptoms of thromboangiitis obliterans, and in another case the diagnosis of erythromelalgia was made. In 3 other patients symptoms suggesting erythromelalgia, i.e. pain in the legs, aggravated by heat and dependency and improved by cold were present, and at times became a prominent complaint.

An interesting feature was the marked tendency to bleed, especially following operative procedures, however simple. Thus in Case 1 there was marked bleeding from a gastric ulcer; in Cases 3, 10, 11, 12, 17 and 19 severe bleeding from the gums occurred after dental extraction, necessitating packing and suturing in several instances. In Case 19, severe bleeding with the formation of a hematoma in the gluteal muscles occurred after an intramuscular injection; in Case 11, large hematomas in the incisional wound formed after appendectomy, and there was a great deal of oozing at the time of operation.

The most constant feature of the symptomatology was, however, the multiplicity of symptoms. Thus, it was quite unusual to find the patient complaining of only two or three symptoms; in most cases, symptoms referable to every part of the body were described.

Salient Physical Signs. A plethoric appearance of the face, with dusky, purplish-red lips, congested conjunctival blood vessels and red ears was present in every instance and was usually responsible for the diagnosis being suspected. The color, to use Osler's phrase, was as " red as a rose " in the summer, but tended to become much duskier and more cyanotic in the winter. The hands participated in the general plethoric appearance and were often beefy red in appearance; in the winter when the patient first appeared from outdoors, they were usually blotchy and blue, gradually becoming unnaturally pink on exposure to the warm air. The feet also showed the same phenomena.

Another constant sign was the presence of greatly distended retinal veins, their deep blue coloration contrasting sharply with the red of the arteries. Congested buccal mucous membranes were common to all cases. The tongue was usually large and thickly coated; in 10 cases, it was in addition deeply fissured, i.e. geographic.

A palpable liver was present in 15 instances; usually it was felt about two fingers' breadth below the right costal margin but at times, as in Cases 11 and 12, it was unusually large, extending to the umbilicus, and quite tender. In both of these cases the chief complaint was of pain in the right side of the abdomen, diagnosed in one case as appendicitis, in the other as gall bladder disease. A palpable spleen was present in 16 cases. It was firm and elastic in the early cases, extending from one to four fingers' breadth below the left costal margin; in the long-standing cases, it became extremely hard and occasionally extended to the pelvic brim. In four cases the spleen could not be felt.

The blood pressure reading was of great interest because of the statement so commonly made that the blood pressure in polycythemia is normal.[14]

In 11 cases, it was above 140 mm. Hg systolic, and in 7 instances was 170 mm. Hg or over. Readings of 200 mm. or over were found in three cases. Thus hypertension was present in the majority of the cases. Gaisböck,[15] some years ago, discriminated a special group of cases of polycythemia, distinguished by hypertension and lack of splenomegaly. He stated that true polycythemia was always associated with a normal blood pressure. It may be noted from table 2 that all of our cases with hypertension also showed splenomegaly.

Other abnormal physical signs were present in many cases: various types of cardiac lesions, certain neurological findings, such dermatological manifestations as hemangiomata, and vascular nevi. The outstanding features were, however, associated with the "plethora vera" of the ancient writers: red face, hands, and feet; congested lips, buccal mucous membranes, conjunctivae; dilated retinal veins; enlarged spleen and liver. As noted below, these were in all probability the results of a chronically overdistended vascular system due to an increased blood volume.

Laboratory Data. Certain of the laboratory data are recorded in table 3. These will not be extensively commented upon here, but it may be noted that (1) the hemoglobin percentage varied from 104 to 170 per cent of normal, (2) the red cell count from 6.70 to 11.0 million per cu. mm., (3) the white cell count from 8,700 to 21,300 per cu. mm., (4) the platelets from 594,000 to 2,850,000 per cu. mm., (5) the polymorphonuclear cells from 74 to 93 per cent, (6) the total blood volume from 5,450 c.c. (after hemorrhage) to 17,500 c.c., (7) the basal metabolic rate from — 19 per cent to + 50 per cent. The urine usually showed albumin and at times casts (cf. Gram[16]), and the blood non-protein nitrogen was at times elevated above 40 mg. per 100 c.c. Thus, despite the rather marked variability in findings, the following was true of the great majority of the cases: an increase in the hemoglobin, the red cell count, the leukocyte count, the polymorphonuclear percentage, the platelet count, and blood volume. Microscopic examination of the capillaries at the nail bed showed uniformly an increased tortuosity and distention of the capillary loops, most pronounced in the venous limbs.

Sternal bone marrow biopsy was performed in eight cases. In every instance the marrow showed a generalized hyperplasia involving *all* of the cellular elements: normoblasts, myelocytes, and megakaryocytes (i.e. "panmyelosis"). In some instances, the increase in megakaryocytes was very striking, as many as 6 to 10 megakaryocytes being seen per high-power field.

The Diagnosis of Polycythemia

Enough has already been stated to indicate that patients with polycythemia may be overlooked for years, and it is likely that many cases are never correctly diagnosed but masquerade under the diagnoses of neurasthenia, various types of peripheral vascular disease, hypertension, heart disease, and nephritis. As in many other rather uncommon diseases, the diagnosis may be overlooked unless it is considered; it is possible, however,

to obtain definite suggestions from the history or the physical examination which may lead one to suspect the diagnosis.

The racial origin of the patient is important. All our cases were Jewish. The high incidence of polycythemia among Eastern European Jews was first pointed out by Reznikoff, Foot, and Bethea.[5] In a series of 134 patients, 47.8 per cent were Jews of Eastern European origin whereas the same racial element accounted for only about 9 per cent of the same general hospital population. In our own series, only two were other than Russian or Polish Jews. The material is of course drawn from a Jewish hospital and a predominantly Jewish clientele; but the contrast between the racial types in our cases of polycythemia and pernicious anemia is striking. Discussion with physicians in charge of the blood clinics at other hospitals of Boston has shown that the cases of polycythemia are ordinarily found among Jewish patients. It should be noted, however, that in the group of cases of polycythemia studied by Blake (Thesis)[17] at the Peter Bent Brigham Hospital (1913 to 1936) the proportion of Jewish patients was only about 14 per cent, which was about the proportion of Jewish patients in the general hospital population.

Other suspicious points in the history are: (1) multiplicity of symptoms, especially relating to the central nervous system, (2) complaint of severe headaches, including migraine, (3) complaints referable to vascular disease of the extremities, (4) history of multiple thromboses, venous and arterial, especially of the extremities, (5) history of severe bleeding following even slight operative procedures. These symptoms although not pathognomonic may lead one to suspect the possibility of polycythemia.

In the physical examination, one looks particularly for high facial coloring, the appearance of reddish cyanosis, highly colored mucous membranes and conjunctivae, dilated retinal veins, a thickly coated and fissured tongue, a large spleen and liver, thick red hands and feet, and hypertension. Examination of the spleen is particularly important and should be carefully made. Percussion of splenic dullness, if performed routinely, is frequently of service in detecting slight enlargement of the organ which cannot be felt unless it is about twice its normal size. Palpation, unless systematically done, may result in failure to feel the spleen entirely. The location of the spleen varies considerably; it may be felt far out towards the flank or near the epigastrium; at times, instead of occupying its usual anterior position, it is situated rather deeply; at times, paradoxically enough, it is so large that the observer in placing his hand just under the costal margin does not feel the lower pole which may be below the umbilicus.

The final diagnosis is made by performance of certain laboratory tests. It is of no value whatever to do a Tallqvist hemoglobin determination in suspected cases, since above the reading of 80 per cent the Tallqvist scale is worthless. The hemoglobin test should therefore be done either by the Sahli or some other relatively accurate method. The erythrocyte count is the central point of the diagnosis and will, with rare exceptions, as discussed

below, immediately confirm or disprove the clinical impression. Before further consideration of polycythemia is entertained, the count should at least be 6.0 millions per cu. mm. The leukocyte, differential, and platelet counts are important in indicating general bone marrow activity. Particularly is this true of the platelet count, which we have come to rely upon as of great importance in diagnosis. Platelet polycythemia ("thrombophilia") has in certain cases been the outstanding feature. Other tests of value are the hematocrit determination, which should be done in every suspected instance, and the blood volume. Estimation of the blood volume [18] has occasionally proved of confirmatory importance in diagnosis of the doubtful case. The normal total blood volume is about 85 c.c. per kg. of body weight or about 5000 to 6000 c.c. It varies directly with the height and weight but especially with the surface area. The plasma volume is normally about 2700 c.c. and about 50 c.c. per kg. In polycythemia vera, as Rowntree and Brown [18] have pointed out, one of the constant features is the striking elevation not only in the total blood volume but in the cell volume ("polycythemic hypervolemia"). It is due to this great increase in blood volume—the general plethora—that the majority of the symptoms and signs are undoubtedly present.

Examination of the capillaries at the nail bed may occasionally be of importance. In polycythemia vera, as pointed out by Brown and Giffin,[19] the capillaries have a characteristically altered appearance: they are very large, tortuous, dilated, and exhibit great distention of the venous limbs. It should be noted that these changes correspond closely to the condition of the retinal blood vessels which show marked dilatation of the veins. It is not known whether these changes are secondary to the increased blood volume or "primary" and thus part of a circulatory abnormality which may be the etiological factor in the disease.

The sternal bone marrow biopsy may occasionally be of diagnostic value and is always of great interest from the pathological standpoint. In every case of polycythemia the marrow is intensely hyperplastic, all the cellular elements—red, white, and megakaryocytic—participating. Of diagnostic importance in certain cases is the extremely large number of megakaryocytes which crowd the sections. Reznikoff et al.[5] have pointed out that the capillaries and arterioles of the marrow show much thickening of the intima and media, which they believe leads to an increased degree of anoxemia of the marrow and thus to polycythemia.

In summary, there are certain symptoms, signs, and laboratory tests which when pieced together spell the diagnosis of "primary" or "true" polycythemia. We have come to rely upon the following group of data as being of diagnostic value:

Symptoms: Headache, vertigo, visual disturbances, colored scotomata, paresthesias
Symptoms referable to vascular disturbances of the extremities
History of profuse hemorrhages after minor trauma
History of venous and arterial thrombosis
Multiplicity of symptoms

Signs: Plethoric appearance of the face and conjunctivae
Dilated retinal veins
Thickly coated and fissured tongue
Splenomegaly, hepatomegaly
Red hands and feet

Laboratory: Elevated erythrocyte count (above 6.0 million per cu. mm.)
Elevated hemoglobin percentage
Elevated leukocyte count
Elevated polymorphonuclear percentage
Elevated platelet count
Elevated hematocrit
Elevated blood volume
Distended capillaries
Sternal bone marrow biopsy: Red cell hyperplasia, megakaryocytic hyperplasia
Elevated basal metabolic rate (cf. Bliss [20])

It should be emphasized that not *every* symptom, sign, or available bit of laboratory evidence is present in every example of the disease. We believe that the following minimal data should be present before a definite diagnosis of primary polycythemia is made: plethoric appearance, spleno- or hepatomegaly, definitely elevated erythrocyte count, elevated platelet count, elevated hematocrit. In a doubtful case, the procedures of blood volume estimation and capillary microscopy may be helpful.

Differential Diagnosis

1. *The Doubtful Case.* Chiefly because of our increasing interest in the diagnosis of primary polycythemia we have been led to examine many cases which present certain features suggestive of the disease. The decision for or against the diagnosis has at times been an extremely difficult one and has frequently required a long period of observation during which opinion might often be changed. Among these doubtful cases were the following:

Albert T., a 27 year old Italian attorney, complained of vague aches and pains. For some years his hands had been blotchy, warm, and perspiring, and blotchy red spots frequently appeared on both the hands and feet. Examination showed a healthy appearing young man with warm, moist, blotchy hands and feet. There was no definite plethora, the retinal veins were not distended; and the spleen and liver were not felt. Routine blood studies showed: hemoglobin 96 per cent; red blood cells 6.49 million; white blood cells 7500; polymorphonuclears 57 per cent. Because of the slight elevation in erythrocyte count, several counts were made; these varied from 6.20 to 6.96 million per cu. mm. Other laboratory studies showed: hematocrit 0.55; platelet count 496,000; total blood volume 7500 c.c.; capillary microscopy disclosed marked tortuosity and irregularity in the diameter of the capillaries of some nail beds and narrowing of the capillaries in others. These findings were thought to be consistent with vasomotor instability. It was decided that the diagnosis of polycythemia was not at present justified despite the elevation in erythrocyte count and the slightly increased plasma and total blood volume because (1) the leukocyte count was normal, (2) the polymorphonuclear count was normal, (3) the platelet count was normal, (4) the spleen was not palpable. No explanation for the erythrocytosis was made except possibly on the basis of vasomotor changes of the extremities. Whether the

diagnosis of polycythemia vera will become more evident in future years remains to be seen.

David S., a 60 year old Russian-Jewish tailor, complained of burning pains in the feet aggravated by exercise, relieved slowly by rest. Examination in 1934 disclosed a slightly plethoric appearance, spider telangiectases of the face, moderate emphysema of the lungs, slight cardiac enlargement, blood pressure 170 systolic and 100 diastolic, irregular blotches of the feet, readily palpable dorsalis pedis arteries. The blood findings were: hemoglobin 92 per cent; red blood cells 5.23; white blood cells 10,000 to 13,500 with 67 per cent polymorphonuclears. The patient improved with rest in bed. In 1935 he was referred to the Blood Clinic because of possible polycythemia. At this time, examination showed a somewhat plethoric man with slight cyanosis of the lips. The retinal veins were not distended, and the spleen and liver were not felt. The blood findings were: hemoglobin 98 per cent; red blood cells 5.53; platelet count 1,680,000 to 1,960,000; hematocrit 0.52; blood volume 4900 and 5200 c.c. It was felt that the findings were at present inadequate to justify the diagnosis of polycythemia vera: the red cell count showed no definite elevation, the spleen was not palpable, and the blood volume was not elevated. The circulatory changes in the extremities in association with readily palpable arteries and very high platelet count suggested, however, the possibility of multiple small thromboses on the basis of a very high platelet count (cf. Nathan W., Case 15). Further follow-up studies are essential in determining this possibility.

Philip Z., a 27 year old Jewish glazier awaiting herniorrhaphy, was referred to the Blood Clinic from the Surgical Service because of suspected polycythemia. In addition to a very plethoric appearance, a red cell count of 6.16 million had been found. The patient said he had "always" had a red face and hands, which became blue with cold and very red with warmth. Otherwise, he had no symptoms except those referable to the hernia. Examination disclosed an extremely red-faced individual with a slight tinge of cyanosis. The conjunctival blood vessels were markedly congested and the retinal veins slightly distended. The spleen and liver were not felt. The hands and feet were deeply red and somewhat cyanotic. The blood findings were as follows: hemoglobin 100 per cent (Sahli); red blood cells, 6.08, 6.16, and 6.70 million at successive examinations; white blood cells 5700; polymorphonuclears 68 per cent; platelets 630,000; hematocrit 0.51; blood volume 6200 c.c. Because none of the findings except the erythrocyte count were at all suggestive of polycythemia vera, the operation of herniorrhaphy was performed; no unusual bleeding took place. This case must be classified as an example of erythrocytosis, possibly normal, possibly associated with some disturbance of the vasomotor system (cyanotic appearance of the face and hands). Whether this case is a very early example of polycythemia remains to be seen.

Dr. S., an Irish-American physician, aged 52, was referred by a neurologist for study of a possible hematological abnormality. In October 1934 and February 1935 he had typical epileptic convulsions. A physician in October 1934 found, in the course of routine laboratory work, that the hemoglobin (Tallqvist) was 70 per cent and the red count 6.50 million. Another physician, in evaluating these data, advised the patient to take iron because of "secondary anemia." Several hemoglobin estimations by the Tallqvist method gave readings in the vicinity of 70 per cent. An intern at the physician's local hospital told the patient he had "hypochromic anemia" and advised even more iron. A neurologist failed to find evidence of anemia and made the diagnosis of idiopathic epilepsy. The patient stated he had had a "high color" for many years and for 13 years had had "indigestion" with a sense of fullness in the right upper quadrant and much belching.

Examination disclosed a large plethoric appearing man. There was definite reddish cyanosis of the lips and buccal mucous membranes. The conjunctivae were reddened and there was dilatation of the fundal veins. The edge of the liver was felt

three fingers' breadth below the right costal margin; the spleen could not be felt. The hands were large, blotchy, and the finger tips were bluish. The blood pressure was 144 to 160 systolic and 90 diastolic. Neurological examination was negative.

The urine showed no albumin, sugar, or casts. The blood showed: hemoglobin 107 per cent (Sahli); red blood cells 6.70 million; white blood cells 7500; differential count: polymorphonuclear cells 74 per cent, lymphocytes 19 per cent, monocytes 7 per cent; platelet count 680,000.

He was given phenylhydrazine hydrochloride at first 0.150 gm. daily, then 0.030 gm. daily, and later 0.030 gm. two to three times weekly. This effectively controlled the hemoglobin and erythrocyte counts. About a month after the erythrocyte count had reached a normal level, the patient's digestive symptoms had completely gone and the liver edge could not be felt. The epileptic attacks continued although they gradually became much diminished in severity and lessened in frequency. For 11 months he had complete freedom from attacks, which then recurred, even though the hemoglobin and erythrocyte counts were at normal levels.

Although this patient was first considered a definite but mild example of polycythemia, he was later placed in the doubtful group because (1) the convulsive symptoms recurred even though the erythrocyte count was retained at a normal level, (2) the leukocyte and platelet counts were normal, (3) the spleen was never palpable, and (4) the blood volume was normal.

2. *Polycythemia Secondary to Known Cause.* These cases should not ordinarily offer any diagnostic difficulty. The finding of polycythemia in the presence of a chronic pulmonary lesion such as bronchitis, bronchiectasis, asthma, or of a chronic right-sided cardiac lesion whether acquired or congenital should almost automatically result in the diagnosis of secondary polycythemia. We have studied several patients of this type, some of them typical examples of "Ayerza's disease": cyanosis, polycythemia, chronic right-sided heart failure, pulmonary hypertension, ? pulmonary arteriosclerosis. The blood always shows evidence of arterial unsaturation, a finding never present in true polycythemia. Although the hemoglobin, erythrocyte count, hematocrit, and even blood volume may be as greatly elevated as in polycythemia vera, there is usually no elevation of the leukocyte, polymorphonuclear, or platelet counts.

Comment

The diagnosis of a condition seen only rarely in everyday practice usually rests first upon thinking of the possibility of its presence and second upon attempting to prove or disprove this by appropriate tests. We gradually become familiar with our errors in diagnosis which may often be directly traced to failure to think of a given possibility. Too often we are accustomed to make the obvious diagnosis and to disregard the possibility that "hypertension," "menopause," or "migraine" might in reality not be the ultimate diagnosis but rather symptomatic expressions of some more general and more serious organic disorder. The first element in the diagnosis of a rare disease is in the suspicion that it might be present. In the case of polycythemia, this suspicion is frequently obtained at the first interview with the patient. A plethoric individual should always be suspected. Multi-

plicity of symptoms, persistent headaches, vascular disorders of the extremities should make one at least wonder about the possibility of polycythemia.

Once suspicion has been aroused, careful search should be made in the history, the physical examination, and the laboratory data for proof of presence or absence of the condition. Whatever the cause of the disease may be, it is certain that the continuous overproduction of red blood cells results in great overdistention of the entire circulation and stasis of blood in the vessels with the production of the many symptoms and signs which have been listed. The physical examination should lean heavily upon search for the evidences of an engorged circulation. The laboratory data will be the determining factors. No reliance whatever can be placed on a Tallqvist hemoglobin test alone; a red cell count at least must be done. If this is only slightly elevated, it should be repeated until a level is obtained. In doubtful cases particularly, the remainder of the laboratory data is of utmost importance, the leukocyte and polymorphonuclear counts and particularly the platelet count being determining factors. Examination of the capillaries at the nail bed and estimation of the blood volume may be differential features in certain cases. No one test, except possibly a constantly and greatly elevated erythrocyte count is of pathognomonic diagnostic significance. In doubtful cases, all the factors pointing to polycythemia should be balanced with those pointing against the diagnosis; it should be appreciated that certain of these factors may be lacking. To summarize: the diagnosis of polycythemia, at first suspected by the patient's appearance and symptomatology, is confirmed by the physical examination, and finally made or disproved through certain simple laboratory procedures.

Summary and Conclusions

1. Polycythemia vera is probably more common, particularly among Jews, than is ordinarily suspected. Its apparent rarity may, in some measure at least, be due to frequent lack of recognition.

2. The disease may masquerade for months to years under many different guises; among others may be listed neurasthenia, migraine, cardiovascular and renal disease, gastrointestinal disorders, and peripheral vascular disease.

3. The diagnosis of polycythemia vera in a plethoric individual may be suspected from certain points in the history: multiplicity of symptoms, vascular disturbances of the extremities, symptoms referable to the nervous system. Physical examination may confirm the first impression of possible polycythemia by the finding of dilated retinal veins, splenomegaly, a thickly coated fissured tongue, and red hands. The final diagnosis is usually made by the laboratory data.

4. The laboratory data in typical cases show not only an elevated erythrocyte count but an increase in all the elements formed in the bone marrow, i.e. leukocytosis, increase in polymorphonuclear cells, and a high blood

platelet count. The hematocrit and blood volume show increased values. Albuminuria is commonly found, and occasionally casts are present. The blood non-protein nitrogen is frequently slightly elevated.

5. Certain borderline, doubtful, or early cases of polycythemia are difficult of exact diagnosis. In these, recourse must be made to repeated studies over a long period of time. The final diagnosis is made by careful consideration of all the various factors in the history, the physical status, and the laboratory examinations.

6. The greatly overdistended circulation of polycythemia results in symptoms referable to many bodily organs. For this reason, polycythemia vera should be considered in the differential diagnosis of such unrelated conditions as neurasthenia, brain tumor, migraine, chronic nephritis, vascular hypertension, chronic cardiovascular disease, peptic ulcer, peripheral vascular disease, and even hemorrhagic diathesis. When the Tallqvist hemoglobin scale is discarded and use of the red blood cell count increased, the number of diagnostic errors should diminish.

Appendix

The use of an iron deficiency regimen in the treatment of polycythemia.

We first utilized this method following our experience with Case 1.[8] The sustained diminution in hemoglobin which followed several severe hematemeses and the use of the Sippy diet was thought to be due to the development of an iron deficiency state. In a series of 10 successive cases of polycythemia, previously poorly controlled by phenylhydrazine, acetylphenylhydrazine, roentgen-ray therapy, and other measures, there was complete clinical and symptomatic relief for 6 to 24 months following the induction of an iron deficiency regimen. This is accomplished by systematic venesections. The use of a diet poor in iron is probably of value in maintaining the iron deficiency state. An average case with hemoglobin of about 150 per cent, erythrocyte count of about 9–10,000,00 per cu. mm., and hematocrit of 65 to 70 per cent requires two venesections weekly for three to four weeks, rarely longer. The hemoglobin is reduced to less than 85 per cent, the hematocrit to less than 48 per cent, and the red cell count to less than 5.5 million. The hemoglobin and hematocrit readings are the important factors in the follow-up of the case, the erythrocyte count being of secondary importance. The red cells become hypochromic and microcytic, i.e. a hypochromic, microcytic "anemia" develops. The marrow continues to produce large numbers of cells, and the erythrocyte count may increase gradually to levels of 6 to 7 million or over, but for several months without further therapy the total circulating mass of red blood cells [9] (which depends upon the hematocrit and blood volume) remains low. When finally, the hemoglobin and hematocrit return to high levels and symptoms recur, only a few venesections are necessary to restore the state of iron deficiency. The diet given contains no meat or eggs and has an iron content of approximately 6 mg. per diem.

Patients on a normal iron intake (12 to 25 mg. of iron daily) usually require venesections at shorter intervals than those on a deficient iron intake.

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SOME ASPECTS OF THE PSYCHONEUROSES *

By Annette C. Washburne, M.D., F.A.C.P., *Madison, Wisconsin*

For practical purposes the psychoneuroses may be viewed as " exhibitions of maladjustment " of the individual to his environment. The term maladjustment has been subject to considerable criticism and discussion. Some have interpreted it as applying only to the reactions of the individual to situational factors, others have used it as a yardstick in the differentiation of the psychoses and the psychoneuroses, while to many the term is merely an unsatisfactory ambiguity.

In its broadest sense it would appear that maladjustments may involve *physiological* as well as *psychological* considerations—reactions of the total organism to environmental changes interpreted as hostile or threatening to the safety of the whole. Environment may be exogenous or endogenous. In the former case, it is composed of situational factors which confront all human beings, sex, home, health, race, money, career, religion and social life; factors which swing from assets (when satisfactory adjustments are made) to liabilities (when maladjustments occur). These situations are exogenous in the sense that while they profoundly affect the individual they also involve other people, impose abstract ideas and bring into play the inter-reactions of a person to a group.

Endogenous environment comprises a vast physiological pattern, the physique of the individual, his endocrine reactions, autonomic nervous system, biochemistry, and somatic responses. Independent in name only the inter-relationship of these factors to each other and to the situation as a whole is so closely knit as to discourage separation (chart 1).

The individual responding to a strong emotional stimulus does so to a greater or lesser degree through the medium of these patterns. The amount of response will be in proportion to the adequacy or inadequacy of the whole. Thus the psychopath is characterized, as Kahn [1] has indicated, by a quantity rather than a quality reaction and his psychopathic tendencies measured through the mounting sum of his instability, excitability and anti-social tendencies. The *quality* of the response will on the other hand be colored and perhaps determined by the individual's *physiological* patterns.

Confronted with a difficult situation, individuals tend to respond by (1) either facing it and attempting to reach a solution—normal reaction, (2) by refusing to meet it and resorting to distractions, as a cover up—extraverted reaction, (3) by withdrawing within themselves—introverted reaction, (4) by taking refuge in ideas of persecution—paranoid reaction, or (5) by demonstrating such an exaggerated response that the original stimulus or

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situation is lost sight of—hysterical reaction. Combinations of these patterns in varying degrees are not infrequently observed although it is probably correct that one of them tends to predominate. This major pattern has been shown in many instances to possess a relationship to the physical build of the individual. Thus the asthenic leptosomic person often demonstrates introverted tendencies, the pyknic, extraverted ones and the athletic

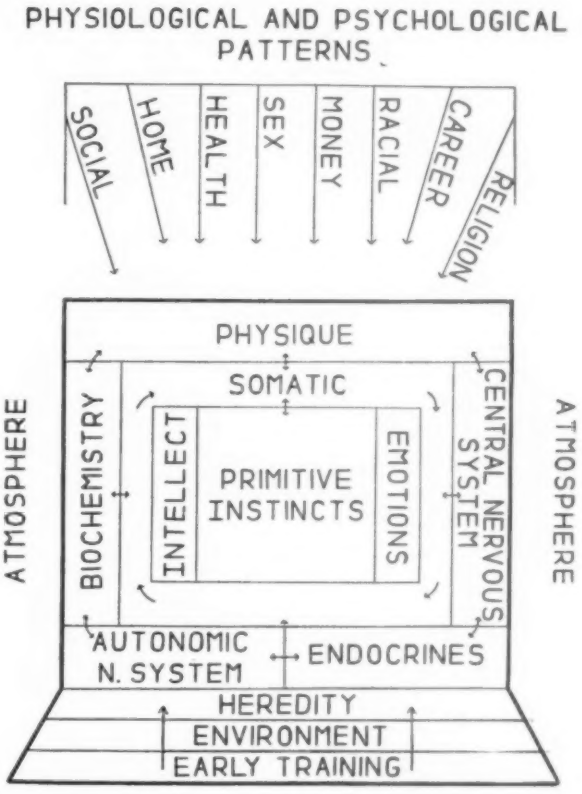

CHART 1. The heavy black line encloses the physiological and psychological patterns present in human beings. Disturbances or alterations in these, either alone or in combination with others may play a part in the adjustment of the total organism. Their inter-relationship is indicated by the arrows. Various situational factors are enumerated as well as the influence of barometric fluctuations, humidity, etc., which are grouped together under the term 'Atmosphere.'

type paranoid reactions. Psychological patterns may be conceived of as a framework from which a mental emotional response appropriate to the individual's make up, will be projected.

Consideration of these points brings into question the advisability or even the possibility of differentiating the organic response from the functional. Definitions fail to clarify the issue since we have no accurate means of determining when one reaction has ceased or another begun. Thus we

are aware that chronic anxiety states not infrequently result in somatic pathology, and that organic disease may be accompanied and in some cases overshadowed by emotional reactions. Conflicts may be expressed through physiological as well as psychological means, frequently through a mixture of the two (chart 2).

Recent advances in the fields of biochemistry and neural physiology point even further away from the functional—organic differentiation. Thus electroencephalographic tracings have demonstrated rhythmic disturbances in certain "functional" conditions,[2] shifts in the mitogenetic radiations of the blood have been reported in neurasthenic states [3] and an increasing number of publications call attention to organic changes in the diencephalon in autopsied 'functional psychoses.'[4]

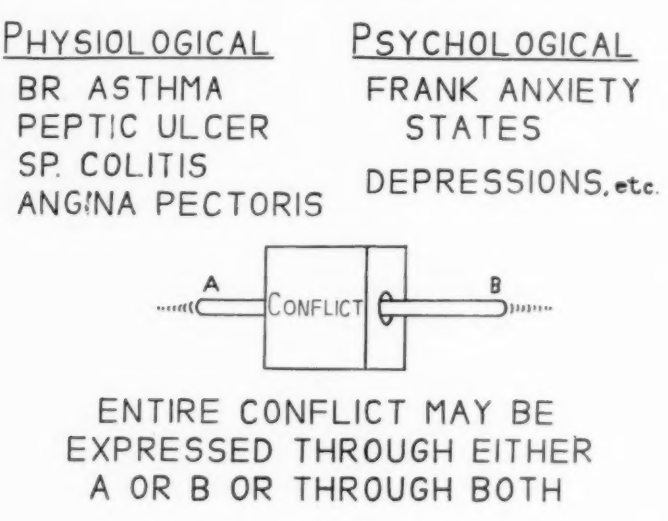

CHART 2.

A stimulating article by Papez [5] considers an anatomical mechanism responsible in part at least for emotional elaboration. His theory proposes that "the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotions as well as participate in emotional expression." Experimental work on animals together with clinical observations in the human lend support to this interesting conception.

In view of the increasing evidence for a biological conception of the psychoneuroses, it would appear that rigid distinctions between "functional" or "organic" are not only difficult but not without danger in that they tend to neglect the alternate consideration. Thus cases which are easily labelled hysteria may later demonstrate brain tumors, encephalitis, multiple sclerosis or other underlying pathology. In the presence of strong hysteroid mani-

festations it is not difficult to overlook or misinterpret neurological or physical signs. The problem more correctly resolves itself not into "*Is this* functional *or* organic" but rather "How *much* is functional and how *much* organic." It is understood of course that "much" refers to an estimate rather than a strict evaluation.

The psychoneurosis may be viewed as a pathological expression of an inward conflict or as previously stated, an exhibition of maladjustment. It is not therefore a meaningless or tiresome reaction nor should it be interpreted as "imagination" or malingering. The latter constitutes a separate group possessing etiology and psychopathology peculiar to itself.

In the psychoneurosis the etiological conflict may or may not be known to the patient. Where it *is* known the reaction has been termed a *suppres-*

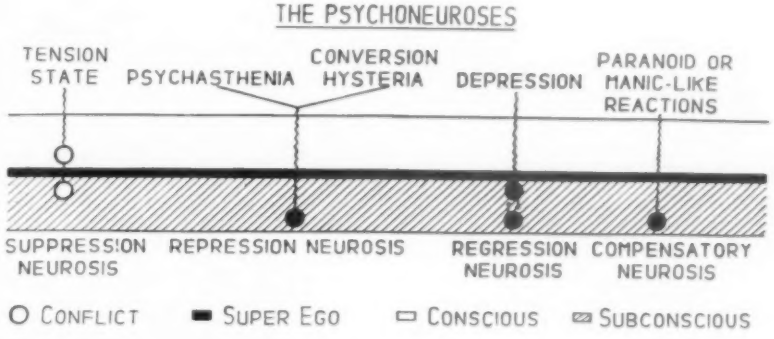

CHART 3. Four types of the more common neuroses are illustrated together with certain of their psychopathological aspects. When the individual is unaware of them the conflicts are shown deep in the subconscious mind. In the case of the suppression neurosis the conflict is indicated as lying in the conscious mind and "just below the surface" of the subconscious since here the individual is "vaguely to entirely aware" of its nature. The form in which the neuroses are presented to the outer world is illustrated in the top line as "Tension State," "Psychasthenia," etc.

sion neurosis (chart 3). Here the individual, though vaguely to entirely aware of the basic difficulty, is for some reason unable to express it fully *as such* and the suppression neurosis or psychoneurosis serves as the only means of outlet. Suppression neuroses are characterized physically by signs of increased tension. The syndrome which has been well outlined by Muncie[6] includes insomnia, "jittery" sensations, gastrointestinal disturbances, constriction headaches, palpitation, etc., all evidences of autonomic disturbance. Psychologically the patient presents an agitated depression.

Clinical Example. Mrs. A. B., aged 24, was referred because of the above physical symptoms which had developed within the past four months. Complete physical, neurological and laboratory studies revealed nothing of significance. The social history developed very little on first questioning. The patient insisted that her marriage of five years' duration had been entirely happy. She had never been pregnant but seemingly had no regrets. It was many weeks before the patient was willing to admit the significant conflict, namely that marital relations had never been consummated

due to impotence on the part of the husband. The patient had spent five years of frustrated sexual life subjected to many indignities by the husband who had threatened suicide if she ever discussed this. Her own sense of shame and inadequacy lent additional impetus for silence. The patient saw no possible connection between her physical symptoms and the marital conflict. Two years of treatment (which included divorce) have resulted in a good recovery. In this case the patient obviously was aware of the conflict but unwilling to admit it and unable to understand its outward manifestations.

There are on the other hand individuals who are entirely *unaware* of the etiological difficulty. These cases are termed *repression neuroses* or psychoneuroses. The unawareness may be the result of several factors: 1. The original psychic trauma is not infrequently one which occurred many years previously and the passage of time has served as a "cover up." 2. As Freud [7] has pointed out, at the time when the trauma occurred the patient was unable to find either adequate expression or a solution. 3. As a result of this, the difficulty was not faced but was thrust back into the subconscious mind where it gradually assumed different proportions through its association with other memories and conflicts. Difficulties which the individual seeks in this manner to bury and "forget" act as foreign bodies. Sooner or later their presence makes itself known, most frequently through physical symptoms acting as symbolic manifestations of the hidden conflict.

The repression neurosis expresses itself either in the form of phobias and compulsions (psychasthenia) or in the development of functional blindness, deafness, aphonia, paralysis, etc. (conversion hysteria). Physically the psychasthenic demonstrates tension symptoms, the conversion hysteria complaints referable to the region involved. Psychically the former group show agitation restricted for the most part to the dominant phobia. The conversion hysterias typically show *no evidence* of mental or emotional distress, the conflict being totally converted into and expressed through the blindness, paralysis, etc. Such patients are usually cheerful to the point of euphoria taking a hearty interest in their major "physical" complaint.

Clinical Example. 1. Psychasthenia. Mrs. T. E., aged 42, was referred because of a cancer phobia. The patient was an intelligent woman who had had nurses' training. Present complaint had developed two years previously when a hysterectomy had been performed for fibroids. Complete examination at this time and on numerous subsequent occasions had failed to reveal any evidence of malignancy. The patient, however, was convinced she had cancer. This she had variously located in the pelvis, the small intestine, the stomach and more recently the sacral spine. The patient was tense and agitated concerning her phobia and its effect on her future. At the end of a conference she was usually able to rationalize—even to laugh, about her 'moving malignancy,' but the next day the fear tended to recur. The patient characteristically would state that she knew the fear was groundless, that nevertheless she could not help it, that perhaps the doctors were mistaken or were not telling her the truth. Previous history demonstrated a tuberculosis phobia 20 years before. The patient denied any known conflict, evading, however, certain questions pertaining to her early home life and generally maintaining the attitude, 'I'm not a neurotic so I must have cancer.' Prolonged investigation brought to light a markedly hostile attitude toward

her mother whom she had always considered a 'nervous neurotic,' and whose numerous complaints irritated the patient excessively. Of late years the husband had been forced through business to spend an increasing period of time away from home. It became evident that the patient bitterly resented this though she had made no complaint. The cancer phobia therefore served a dual purpose: 1. If she had cancer she would be in a different category from the mother, in other words, 'really ill and not neurotic'; and, 2. If she had cancer her husband would be forced to stay home. This type of reasoning had, needless to say, never been indulged in by the patient and its gradual unfolding met with resistance. This patient has shown moderate improvement during two years' treatment, the cancer phobia being less constant.

Clinical Example. 2. Conversion Hysteria. M. B., aged 28, was referred because of paralysis of both legs. Present complaint was of three months' duration and had been sudden in onset. There was no physical or neurological history of significance. Complete examination including lumbar puncture and roentgen-rays of the spine was negative. The patient was calm and in no sense worried or apprehensive. During the examination she was overly anxious to help. Social history gradually developed the following picture—the patient had lived on a farm with two small sisters and her widowed father to whom she was deeply attached. One night 10 years previous to the onset of the present difficulty the father suffered a severe heart attack. Having no telephone and the car being out of order the patient rode a bicycle three miles to the nearest physician. By the time the doctor arrived the father was dead. The patient's grief was profound but financial worries became so pressing that for the next nine years she attempted to forget the whole picture, seeking feverish distraction in work. One month before the onset of the paralysis unexpected financial aid was received. The patient for the first time had an opportunity for leisure of a sort. Recollections of her father and his death became more acute. One morning she awoke unable to walk. Continued investigation gradually brought to light a pathological sense of guilt which the patient felt for her father's death. She had "not ridden fast enough," if she had "pedaled more rapidly the doctor would have arrived sooner" and her father would have been saved. It was therefore her fault that he had died. For obvious reasons the patient had been unwilling to contemplate this patricidal aspect. As the situation was slowly worked out she made a complete recovery. It is interesting that the legs, the principal offenders (in the ride to seek help) were the regions selected for "punishment" by the paralysis.

Another type of reaction is that which takes place in an individual who is also unaware of the nature of the etiological conflict but responds to its disguised manifestations by withdrawal or retreat. Such a picture is termed a regression neurosis. The person drawing within his shell presents to the outer world evidences of fatigue, anorexia, weight loss and general malaise. Psychically there is depression expressed in attitudes of indifference, listlessness, apathy or despair (suicidal attempts being not infrequent).

Clinical Example. Mr. W. A., aged 35, comes in because he feels vaguely unwell. Present complaint began three weeks previously. Physical examination and laboratory studies were negative. Social history revealed that the patient had suffered financial reverses during the past year but had accepted these with a considerable amount of stoicism until he discovered evidence that the reverses were in large part due to the dishonesty of his brother. Unable to accept or face what he felt to be an intolerable blot on the family honor the patient instead of pursuing the matter of settling it in one way or another withdrew into himself, became uncommunicative and listless and developed the picture outlined above. Psychotherapy was successful in establishing improvement.

Seeking relief from an unrecognized conflict through flighty-manic ideas, or through the projection of self hatred or ideas of persecution is termed a compensatory neurosis or psychoneurosis. Physically such individuals tend to have multiple complaints. Psychically their manner in the paranoid type is demanding, arrogant, suspicious and antagonistic; infantile, boisterous and exuberant in the manic patterns.

Clinical Example. Paranoid Type. N. Y., aged 26, white, unmarried male was referred because of difficulty in adjusting himself to his co-workers. An accompanying friend stated that Mr. Y. was becoming a problem in the office due to his overbearing actions. Physically the patient showed evidence of a pituitary gonadal dysfunction—hair growth scanty, feminine contour to hips, prostate smaller than usual. The external genitalia were normal and the testes descended. Psychologically the patient was overly sensitive, sarcastic and suspicious. After several conferences he admitted homosexual activities. Lately he had become fearful of discovery. His paranoid tendencies became exaggerated. His unwillingness to admit a sexual deviation led to a projection of his own ideas of hatred upon the outside world. He had begun to see in each person a potential enemy who was capable of surmising his secret. Feelings of inferiority and fear were compensated by a superiority complex. Psychotherapy and endocrine therapy (prephysin) were helpful in establishing a better mental attitude. There was no change in the glandular picture.

The present state of psychiatric terminology is so confusing that the clinician is not infrequently at a loss for a label. Actually a label is of far less usefulness than an understanding and evaluation of the underlying psychopathology. Summarizing this point certain generalities may be formulated:

1. That a psychoneurosis while constituting an exhibition of maladjustment is also paradoxically,

2. An *attempt* at adjustment. This becomes more evident when it is recalled that the psychoneurotic reaction provides an outlet through which conflicts may find expression. The use of such an outlet represents the patient's attempt to adjust.

3. The frequent involvement of the autonomic nervous system brings with it a train of symptoms which are eagerly seized upon by the patient. Thus tachycardia, anginal pains, increased or reversed peristalsis, peptic ulcers, spastic colitis, muscle tension, etc. become a respectable barrage through which the conflict finds socially acceptable expression.

4. The presence of these symptoms serves as a subconscious alibi for the patient. The man who is sick is excused and decisions, as Adler [8] has indicated, may be postponed.

5. Regardless of descriptive labels certain psycho-mechanisms tend to repeat themselves, and the recognition and evaluation of these appears of far greater significance than hair splitting distinctions between such descriptive prefixes as fatigue neurosis, neurasthenia, sexual, anxiety, occupational, situational, war or prison neurosis, etc. etc. These terms which serve as indications of the dominant symptoms tell us in reality little of the underlying pathology. Actually some 16 psycho-mechanisms are recognized. This

paper has considered four of the more common ones, suppression, repression, regression and compensation. Using this classification of Kempf's [9] the clinician seeks to estimate the degree in which each is present and its relation to future progress. Thus suppression neuroses tend to present a better prognosis than the other types—repression neuroses can usually be cleared of the immediate phobia or hysterical symptoms but there is a strong possibility that these may later be replaced by other fears or fixations. Regression neuroses considered here in only their mildest manifestations may be safely considered as potentially malignant. With their tendencies toward withdrawal, isolation, regression to childish levels, they offer a bizarre and unhealthy reaction. Compensatory neuroses tend on the whole to be benign, particularly the manic types, while paranoid expressions especially if accompanied by signs of disorganization and dissociation may be more serious. It is understood that these four types are not sharply demarcated, that it is quite possible to find evidences of a compensatory mechanism in what is quantitatively estimated to be, for example, a repression neurosis. In such cases prolonged observation coupled with clinical judgment must be relied upon.

No attempt can be made here to discuss the psychoses but attention should be called to a brief differentiation from the psychoneuroses.

1. A psychosis represents a *total failure* in adjustment whereas the psychoneurosis, as has been noted, is *an attempt* at adjustment.

2. A psychosis is a more serious problem than the psychoneurosis since in many cases mental deterioration occurs.

3. A psychosis is a total disorganization of the personality, the psychoneurosis a problem in maladjustment.

4. In a psychosis one finds *exaggerated* versions of the psycho-mechanisms discussed above. Thus compensatory mechanisms in their most extreme form are found in the manic type of manic depressive insanity (benign) and in paranoia (a malignant type of compensation). Regression mechanisms are seen in the depressed form of manic depressive insanity (benign), dementia praecox (malignant), where in the catatonic types, the patient demonstrates complete withdrawal.

The term malignant as employed here has reference to those conditions which show evidence of dissociation, disintegration and deterioration.

The *science* of psychotherapy is based upon three cardinal points: 1. Mental catharsis. 2. Desensitization. 3. Reëducation. The *art* of psychotherapy rests in the ability of the physician to fit these points to the individual case. It is the latter consideration which has been responsible for the accusations of vagueness which are often raised when the psychiatrist is asked to discuss therapeutic measures. It is difficult if not impossible to re-create the time spent with a patient, to present in review the conversation, attitude, mannerisms, etc. which were observed. Yet all of these are integral

parts of the procedure, the outcome of which rests upon the successful interpretation and evaluation of the *patient and his story.*

In a general way, however, after having obtained a detailed history several points may be mentioned:

1. The physician should have in mind several considerations:

a. A careful physical examination properly to rule out demonstrable organic pathology.

b. Bearing in mind that a psychoneurotic element may overshadow and for a time obscure physical disease, repeated physical examinations at different intervals may be indicated.

c. Neurological examination. The possibility of brain tumor or encephalitis as a background calls for a neurological examination, especially ophthalmoscopic studies.

d. Laboratory studies. Where possible serology, complete blood counts, and urine examinations are desirable. Occasionally a basal metabolic rate will be found to have variations from the normal, not infrequently on the hypothyroid side. Changes in blood sugar, calcium, cholesterol, vitamin A content, etc., while of great interest and frequent significance, call for more specialized assistance than is usually available.

The point originally mentioned, of a detailed history, needs further elaboration. During the history taking considerable information can be obtained from observation of the patient's manner, attitude, willingness or unwillingness to touch on certain aspects of the story, etc. Introverted, extraverted, paranoid and hysterical tendencies may be brought out during this time. Physical complaints no matter how bizarre should be later checked as noted above. The physician having obtained the available story and performed a physical examination will be wise to consider the possibility of a psychosis. The differentiation is not always easy; in general, however, certain points may be stressed:

1. A psychosis tends to show more exaggerated reactions than a psychoneurosis.

2. A psychosis often has attending organic pathology—toxic conditions, general paresis, menopause, arteriosclerosis, senility, etc.

3. A psychosis may demonstrate hallucinations, delusions, disorientation and dissociation.

In certain paranoid psychoses where mental deterioration occurs late if at all the problem may require hospital observation.

The first part of psychotherapy, i.e., mental catharsis, consists in encouraging the patient to tell his *entire story and in the way in which he chooses.* The time required will depend upon how much of the conflict is known to the patient and how willing and ready he may be to discuss it. As a minimum several weeks may be required before catharsis is effected, as a maximum, many months. It does not follow that the disclosure of the

etiological conflict is *always* the best therapy. In certain of the regression neuroses (depressions for example) the patient may not be able to adjust himself to the "complete view of the whole." Clinical judgment then is essential in determining in each case how far this first part of therapy should be pursued. Following the disclosure of the etiological conflict an attempt is made to secure desensitization through therapeutic conversations in which the patient is encouraged to look upon his difficulties from different points of view. The purpose of this is to develop perspective, objectiveness and an understanding of the manner in which the conflict developed and its methods of expression. Reëducation is then begun. The patient's future is considered in relation to his present abilities and potentialities. Changes in environment or manner of living may be necessary and advice on the prevention of other neurotic episodes is given. Reëducation of the family is included in this procedure as their sympathetic understanding and co-operation is necessary.

The use of drugs, especially sedatives, is frequently required. In our experience phenobarbital grains ¼ t.i.d. or q.i.d. is a better choice than bromides [10] and has a distinct use in the treatment of tension states. Sodium amytal grains $\dot{i}$ b.i.d. or t.i.d. may also be of benefit. For hypnotics nembutal grains $\overline{iss}$ or sodium barbital grains $\overline{v}$ are recommended. For those unable to take the barbiturate hypnotics, paraldehyde drams $\ddot{\overline{ii}}$ is a good substitute.

In conclusion the question of therapy may be summarized in the following fashion:

1. An individual presenting a picture with psychoneurotic manifestations should be studied from a physical, neurological and when possible, a biochemical endocrine aspect as well as a psychiatric one.
2. If physical neurological or other demonstrable pathology is found this should be treated first.
3. Psychotherapy should be directed at (1) the disclosure of the etiological conflict, (2) the rationalization or desensitization to this conflict, (3) reëducation of the patient.
4. The possibility that one is dealing with a psychosis rather than a psychoneurosis should be carefully considered.

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LUPUS ERYTHEMATOSUS DISSEMINATUS *

By Joseph J. Bunim, M.D., *New York, N. Y.*

Increased attention has recently been drawn by various observers [1-7] to the importance of visceral involvement in acute lupus erythematosus. A greater familiarity with the signs and symptoms of this disease has naturally resulted in a more frequent recognition of this syndrome. Ludy and Carson [8] believe that the incidence has actually increased.

The exact diagnostic criteria have not yet been established, however. This is due not alone to the fact that the etiology is unknown but more so because there seems to be no minimum number of clinical or pathological features that one may expect to find consistently in each case. While cutaneous lesions, arthralgia, polyserositis, endocarditis and nephritis are the commonest attributes of this syndrome, any one or several of these may be absent. Nevertheless, the impression is gaining ground that this syndrome is actually one disease with a fairly clear-cut age and sex incidence, an intermittent course of several months or years, and an almost invariably fatal termination. In defending the entity of this disease one need hardly plead further than to cite rheumatic fever as a precedent.

We have studied a typical case of disseminated lupus erythematosus for 20 successive months from onset to termination. This case is somewhat unusual in that it presents a greater number of the well recognized clinical and morphological features of this disease than is usually encountered in any one single patient.

Case Report

History: Eleanor K., a white American girl of 20, first became ill in September 1937. Her past history was non-contributory. During the preceding summer she had been exposed to a good deal of sunlight on a camping trip and on weekly fishing trips in a sail boat. She stated that even on mild exposure she would develop a sunburn and with it unusual reactions consisting of severe headaches and repeated vomiting. Her illness began with migrating polyarthritis involving practically all the joints of the body and associated with a low-grade fever. This onset was not immediately preceded by exposure to sun. From September to Christmas the symptoms were mild enough to permit her to be up and about. On December 25 she began to vomit and continued to do so about twice daily for two weeks. This was accompanied by anorexia, weakness and mild diarrhea. She later noticed dyspnea, orthopnea, palpitation and precordial pain. One week before admission she developed a sore throat and a cough productive of a sputum which was occasionally blood streaked. During the fourth month of her illness and four days before admission, a skin eruption appeared on both cheeks. This was symmetrical, circumscribed and of a deep reddish-purple color. A physician told her she had erysipelas.

First Admission: The patient was admitted for the first time to the Third (New

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From the Third (New York University) Medical Division of Bellevue Hospital and the Department of Medicine, New York University Medical College.

York University) Medical Division of Bellevue Hospital on January 15, 1938. She appeared acutely and seriously ill, prostrated, feverish, apathetic, dyspneic and orthopneic but not cyanotic. Over both cheeks and ear-lobes were symmetrical, circumscribed, intensely erythematous, superficial lesions covered with a fine scale. The skin over the bridge of the nose was clear. Superficial ulcerations with telangiectasia were present on the soft palate and uvula. The throat was acutely inflamed and the glands of the neck were palpable. Bilateral papilledema was present with superficial linear hemorrhages close to the disc; the retinal venules were slightly dilated and tortuous, but the arterioles appeared normal. The apical impulse of the heart was not palpable; the rhythm was regular and the rate 120 per minute. A presystolic gallop and a systolic blowing murmur were audible over apex and base. P_2 was louder than A_2. Blood pressure was 120 systolic and 60 diastolic. The lungs and abdomen were negative. The neurological status was normal. The temperature was 104° F.

Course: From the fifth day to the beginning of the fifth week petechiae appeared in crops in both conjunctival sacs. On the sixth day a small ulcer developed over the coccyx which advanced rapidly and in the course of a week became an extensive deep necrotic bed sore about 2½ inches in diameter, progressing later to expose the spines of the sacrum and extending into the left ischial fossa. Toward the end of the second week the skin eruption and buccal mucous membrane lesions began to disappear. During the third week she suffered from attacks of paroxysmal dyspnea; no other signs of left ventricular failure were present and the lungs remained perfectly clear. The paroxysms disappeared once the patient was placed in an oxygen tent. She remained in the tent for five days and thereafter suffered no recurrences of dyspnea.

From the fourth through the ninth week the patient was incontinent of urine and feces and throughout the sixth week was comatose and irrational. Her temperature during this period varied between 100° and 105° F. At the beginning of the eighth week her general condition began to improve. She no longer was irrational. She was cheerful and interested in environment. She regained a desire for food. Her temperature, however, ranged between 100° and 103° F. and multiple abscesses appeared in the region of the bed sore. Despite the fact that she felt and appeared much improved, a to and fro pericardial friction rub was heard during the ninth week and persisted for 14 days. Throughout this interval no petechiae could be found and the electrocardiographic tracings (both standard and precordial leads) were within normal limits. With the friction rub an apical systolic blowing murmur and a presystolic gallop were heard.

By the eleventh week few abnormal findings were present. The temperature was normal. The bed sore began to heal rapidly. The cardiac findings were normal except for a rate of 100 per minute and an apical systolic blowing murmur. There were no petechiae. The papilledema and retinal hemorrhages were gone. The skin and mucous membrane were normal. The patient was no longer incontinent. During this week an abscess appeared over the left shoulder but cleared soon after aspiration. The patient had not menstruated for the past six months. She was discharged at the end of the eighteenth week (May 20) after having been up and about the wards with no complaints and no fever for two weeks.

Therapy: Treatment consisted of supportive measures. For the skin and mucous membrane lesions nicotinic acid was tried; 200 mg. a day were given for 10 days beginning January 26. During this period these lesions cleared considerably but they had begun to improve a few days before nicotinic acid was first given, and furthermore, despite this gain, the patient's general condition was growing steadily worse. She did not begin to recover until many weeks after nicotinic acid was discontinued.

Seven transfusions (500 c.c.) were given from the second to the tenth week and each time some clinical improvement was noticed for several days afterwards.

The diet was high in calories and vitamins. Fluids containing sodium chloride and glucose were given parenterally when the patient was unable to take food by

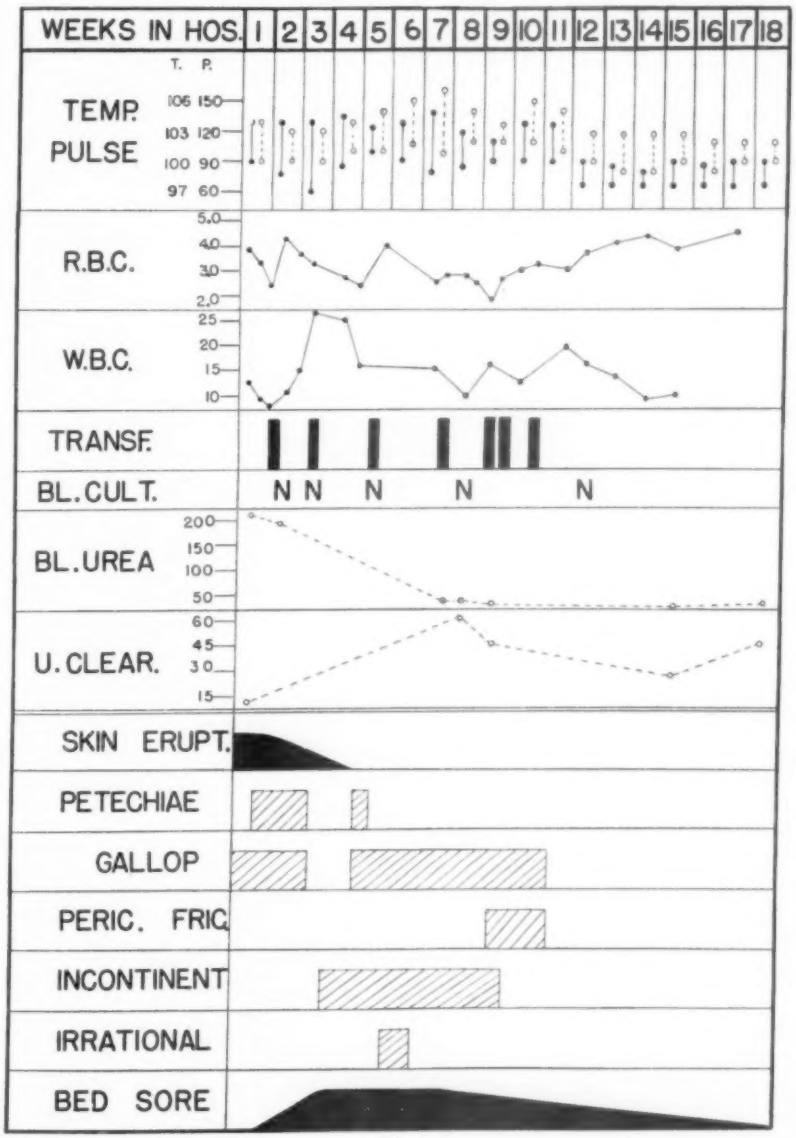

FIG. 1. Chart of the clinical course during first admission.

Hos. = hospital; Temp. = temperature designated in maximum and minimum readings by solid circles; Pulse = represented by open circles; R.B.C. = red blood cell count in millions per cu.mm.; W.B.C. = white blood cell count in thousands per cu.mm.; transf. = transfusions, each block represents 500 c.c.; bl. cult. = blood culture; N = negative; Bl. urea = blood urea in mg. per cent; U. clear. = urea clearance expressed in per cent of normal; peric. fric. = pericardial friction rub.

mouth. The bed sore was treated by daily irrigations with Dakin's solution followed by dry sterile dressings. At no time was sulfanilamide administered. On discharge the patient was warned to avoid sunlight and never to be exposed to ultra-violet lamps.

Renal Studies: On admission, the patient's uncatheterized urine contained 15 red blood cells, 15 to 20 white blood cells and 1 to 2 hyaline casts per high power field. The specific gravity was 1.010 and a faint trace of albumin was present. Five days later the red blood cells disappeared but the specific gravity, determined daily, did not rise above 1.010 until the third week and did not reach 1.020 until the end of the

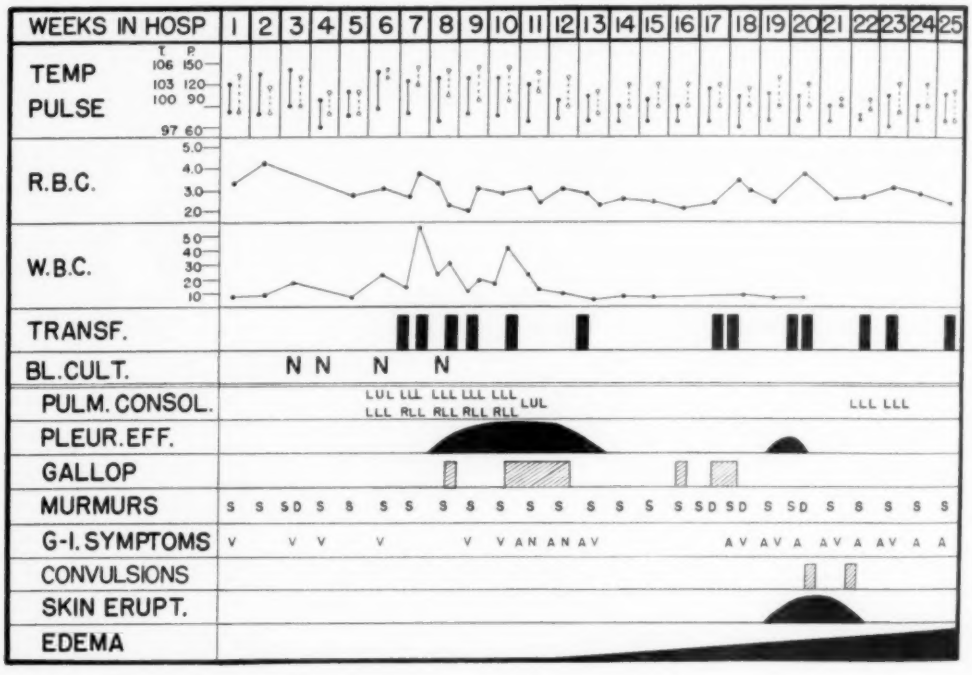

FIG. 2. Chart of the clinical course during last admission.

Hos. = hospital; Temp. = temperature designated in maximum and minimum readings by solid circles; Pulse = represented by open circles; R.B.C. = red blood cell count in millions per cu.mm.; W.B.C. = white blood cell count in thousands per cu.mm.; transf. = transfusions, each block represents 500 c.c.; bl. cult. = blood culture; N = negative; pulm. consol. = pulmonary consolidation; L.U.L. = left upper lobe; L.L.L. = left lower lobe; R.U.L. = right upper lobe; R.L.L. = right lower lobe; pleur. eff. = pleural effusion; S = apical systolic murmur; D = apical diastolic murmur; V = vomiting; A = anorexia; N = nausea.

fourth week. At all times there were numerous white blood cells. During the thirteenth week, when the patient was well on her way to recovery, red blood cells reappeared in the urine. During the seventeenth week an Addis sediment count (calculated as per 12 hours) showed 5,910,000 red blood cells, 2,400,000 white blood cells, and no casts. Two weeks later, on the day of discharge, another sediment count showed 35,980,000 red blood cells, 12,960,000 white blood cells and no casts, thus revealing a marked hematuria.

During the first week the blood urea was 217 mg. per cent and the urea clearance was only 12.8 per cent of normal. On February 7, the blood urea was 194 mg. per cent. On March 4, it fell to 42.8 mg. per cent and on March 8 to 40.6 mg. per cent.

The urea clearance rose on the latter date to 59.7 per cent of normal. This is about the time that the specific gravity reached 1.020. On March 17, April 25 and May 20 the blood urea was 30.6 mg. per cent, 22 mg. per cent and 32.6 mg. per cent, respectively, and the urea clearance was 45 per cent, 28 per cent and 44 per cent of normal, respectively.

At no time did the blood pressure rise above 126 systolic or 80 diastolic.

Bacteriological and Immunological Studies: Blood cultures (aerobic and anaerobic) taken January 22, January 31, February 12, February 18 and April 2 were all sterile. Throat culture (January 18) showed numerous staphylococci and hemolytic streptococci. The culture from the bed sore (February 13) showed diphtheroids, hemolytic and non-hemolytic staphylococci and *B. Coli.* The pus aspirated from the abscess on the left shoulder (March 31) contained hemolytic staphylococci. The cervical smear showed no gram-negative cocci.

The Wassermann reaction was negative. The gonococcus complement fixation test was plus-minus. The antistreptolysin, antifibrinolysin, hemolytic streptococcus agglutinin and precipitin (Lancefield's "C" substance) titers done during the first week and last were within normal limits on both occasions.

Hematological Studies: The red blood cell count on admission was 3,900,000 and the hemoglobin 78 per cent (11.3 gm.). The white blood cell count was 12,650 with 57 per cent polymorphonuclears, 15 per cent lymphocytes, 16 per cent metamyelocytes II, 7 per cent metamyelocytes I and 5 per cent monocytes. Ten days later the red blood cell count fell to 2,420,000 and after a transfusion of 500 c.c., rose to 4,300,000. The anemia was most severe at the beginning of the ninth week when the red blood cell count was 1,800,000 and the hemoglobin 52 per cent (7.5 gm.). With the aid of three more transfusions and an anti-anemic diet, the erythrocytes gradually rose to 4,500,000 and the hemoglobin to 83 per cent (12.0 gm.). The white blood cell count at no time was below 7,300 and during the third week it reached a maximum of 29,600. Roentgenological examination of the lungs was normal. An azygos lobe was noted. The heart shadow was moderately enlarged.

Electrocardiograms taken on seven occasions were all within normal limits, showing either regular sinus rhythm or sinus tachycardia. There was no deviation of the electrical axis and no conduction defects.

Porphyrin Studies: Twenty-four hour urinary porphyrin excretion studies * showed an output of 475 micrograms during the last week of the patient's hospital stay. Six subsequent determinations done a few weeks later showed, however, an excretion of only 35 micrograms per day.

Second Admission: The patient was seen again on September 14, 1938, four months after discharge. She had no complaints except mild joint pains and contraction of flexor tendons of the two last fingers of her right hand. She agreed to enter the hospital for further studies. Her weight had risen from 95 to 131 lbs.; blood pressure 120 systolic and 78 diastolic. The fundi were normal. Heart was normal except for a rate of 110 per minute. Electrocardiogram showed no abnormal changes except ventricular premature contractions. Skin was clear. Alopecia which had occurred soon after discharge was now undetectable. No petechiae could be seen. The red blood cell count was 4,430,000 with 75 per cent hemoglobin (11.0 gm.). The white blood cell count was 5,900 with a normal differential. The platelet count was 124,040. An Addis urine sediment count at this time showed: specific gravity 1.021; pH of 6.8; albumin ++; red blood cell count 11,870,000; white blood cell count 6,740,000 and casts 973,000. The blood urea was 24.4 mg. per cent and the

* Normal porphyrin excretion in the urine varies from 0 to about 100 micrograms per 24 hours. The porphyrins were extracted by the ether-acetic acid-hydrochloric acid method of Fischer and determined as coproporphyrin by comparisons with standard solutions of coproporphyrin spectroscopically and fluorimetrically. The determinations above reported were done by Dr. L. A. Rosenblum.

urea clearance was 75 per cent of normal. The levulose tolerance test and bromsulphalein test showed perfectly normal liver function. Thus, clinically the patient was found markedly improved, though a severe microscopic hematuria persisted. She left the hospital in four days.

Third Admission: During the month of October 1938, she suffered with multiple joint pains and weakness and noted several ecchymotic areas on her skin. There was no bleeding from any of the mucous membranes. On the morning of November 10 she was seized with a sudden, severe, lower abdominal, cramp-like pain followed by nausea and vomiting. She was told by a physician that she had acute appendicitis. On admission to Bellevue Hospital that night there was resistance but no true rigidity over the right lower quadrant, with considerable rebound tenderness. Pelvic examination was negative except for tenderness upon moving the uterus. Several small ecchymotic areas were present over thighs and legs. The right knee and wrist were warm and tender. The cardiac impulse was not palpable, the rate was 134 and a loud systolic blow was heard at the apex. There was no friction rub or gallop. The eye grounds were normal. There were no petechiae, no rash, no splenomegaly or hepatomegaly. The abdominal pain soon subsided but fever and occasional vomiting continued and anemia progressed. Two weeks after admission she developed acute pharyngitis with sudden rise in temperature to 104°. Throat culture showed diphtheria bacilli. Schick test was positive and the control was negative. Since the organisms could not be recovered on successive cultures and since there were no clinical signs of diphtheria, no anti-toxin was given. A week later the temperature again was normal and the patient comparatively free of symptoms for two weeks.

During the sixth week she became seriously ill, cyanotic and dyspneic, and there appeared frank signs of consolidation first in the entire left lung and then in both bases. The temperature rose to 104.6° and the leukocyte count to 56,000. No chill or bloody sputum was present and the cough was unproductive. A throat culture yielded unclassifiable pneumococci so that no specific anti-serum could be given. She did not respond to customary doses of sulfanilamide or sulfapyridine, with blood concentration of free sulfanilamide as high as 11 mg. per cent. She was put in an oxygen tent and after a stormy period of two weeks, during which time she was once again irrational and incontinent, a moderate improvement was observed. The signs of consolidation shifted from one lung to the other during the course of the next few weeks. Severe chest pain now became a prominent symptom and bilateral pleural effusion was noted. Five hundred c.c. of serosanguinous fluid were removed from the right chest during the ninth week and a few days later another paracentesis yielded 350 c.c. No organisms were recovered on culture. The chest signs slowly disappeared and the lungs remained clear for five weeks, when signs of consolidation and fluid re-appeared.

At about this time arthralgia recurred, peripheral edema developed and the liver became palpable. The edema became progressively more severe, was of generalized distribution but most prominent in legs and feet. The liver edge descended to three fingers-breadth below the costal margin. The spleen was not palpable. Conjunctival petechiae re-appeared and on several occasions some observers felt convinced they heard a diastolic rumbling murmur at the apex. A presystolic gallop was present intermittently. Furuncles and subcutaneous abscesses appeared on her back and face. The former bed sore again became extensive. The original butterfly erythematous eruption of the face re-appeared for four weeks towards the end of the course and then faded completely. During this time the optic disc margins again became blurred, but no hemorrhages or exudate were present. First muscle twitches appeared and later she had two generalized tonic convulsions with no localizing or residual signs. Examination of spinal fluid was negative. The major therapeutic problems consisted of combating unyielding anorexia, nausea and vomiting, and a resistant anemia, which failed to respond to a total of 10,000 c.c. of whole blood. Save for a few days of

comparative improvement scattered through 25 weeks of prostrating and wasting illness, the patient continued to lose ground steadily. During the last few days she was irrational and incontinent and complained of chest pain and dyspnea. The bed sore became very extensive, edema increased and now included the face. The abdomen was distended and was thought to contain free fluid in the peritoneal cavity. Tachycardia and gallop were present. The patient died on May 1, 1939, 20 months after the onset of her illness.

Renal Studies: The urea clearance on November 16, 1938, was 30.4 per cent of normal and blood urea was 75.4 mg. per cent. The non-protein nitrogen steadily decreased as follows: December 27—60 mg. per cent; January 18—32 mg. per cent; February 6—33 mg. per cent; March 23—40 mg. per cent; and April 21—38 mg. per cent. An Addis sediment count of the urine, done on November 16, 1938, showed 7,665,000 red blood cells, 465,000,000 white blood cells and 26,000 casts. Fifty-four

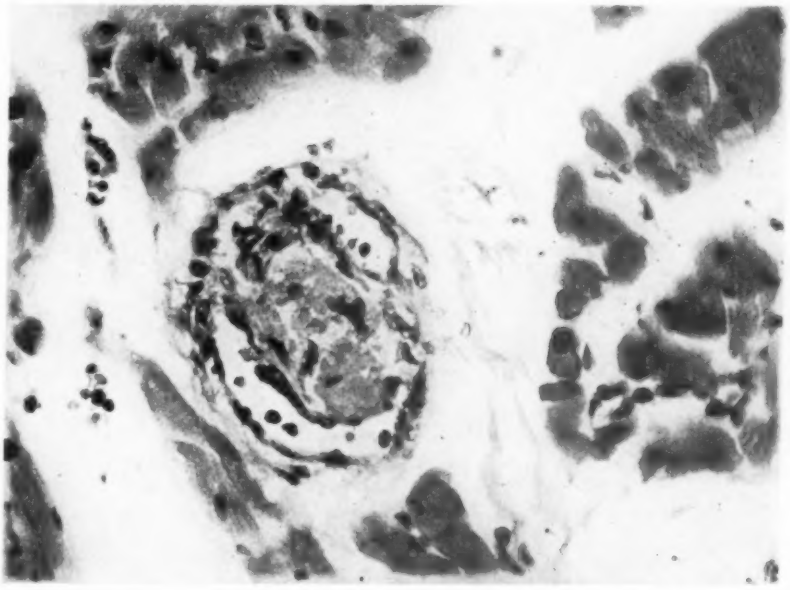

FIG. 3. Photomicrograph (high power magnification) of a section through left ventricular myocardium showing canalyzing thrombotic lesion in a myocardial vessel. The thrombus was composed of granular, pale eosinophilic material lined by endothelial cells.

urinalyses done during this admission showed a specific gravity ranging between 1.006 and 1.020, a persistent proteinuria varying from one to three plus, a few red blood cells and numerous white blood cells per high power field in each specimen. At no time did the blood pressure rise above 150 systolic and 80 diastolic. The average reading was 120 systolic and 60 diastolic.

Bacteriological and Immunological Studies: Blood cultures taken during the third, fourth, sixth and eighth weeks were sterile. As mentioned above, the throat culture on November 23 showed diphtheria bacilli but these could not be recovered on subsequent cultures. From a subcutaneous abscess and facial furuncle *Staphylococcus aureus* was grown. The pleural fluid of January 14, 1939 was sterile, as was the spinal fluid of April 9, 1939.

The Wassermann reaction was negative. The gonococcus complement fixation test was negative. The antistreptolysin, antifibrinolysin and hemolytic streptococcus

agglutinin and precipitin titers done March 19, 1939 were again within normal limits. The Schick test was positive. The colloidal gold curve of spinal fluid was 000 000 0000.

Hematological Studies: The red blood cell count varied between 4,200,000 and 2,100,000, remaining between two and three million in most instances and rising above three million only after one or two transfusions. The hemoglobin ranged between 5.8 and 10.0 gm. per 100 c.c. The white blood count was elevated from the third to twelfth weeks, during the period of pulmonary infection and high fever. Leukocytosis on one occasion reached 56,200, on another 46,200, and on a third 42,650 with an increase in polymorphonuclears and metamyelocytes. During the latter half of her course the white blood count stayed between five and ten thousand with a normal differential. At no time was leukopenia present. The erythrocyte sedimentation rate was elevated.

Roentgen Examinations: The lungs on January 17, 1939, showed bilateral pleural effusion reaching on the left side as high as the subapical region and on the right, filling the lower two-thirds of the chest. There was also a moderate amount of pneumonitis visible in the areas not obliterated by the effusion. As before, the azygos lobe was noted. On April 14, 1939, extensive broncho-pneumonic infiltration was seen in both lung fields.

Electrocardiograms: The tracings which were normal during the first admission and during the first month of this admission showed persistent low voltage during the last two months of life. Tachycardia and premature ventricular and His bundle contractions were the only other abnormalities. There was no deviation of the electrical axis and no prolongation of P–R interval or QRS complex.

Autopsy: Autopsy was performed two hours after death, by Dr. Eugene Clark.

Macroscopic examination: Except for several furuncles on both cheeks there were no facial lesions. Decubitus ulcers were present over the sacrum and both iliac crests. On opening the peritoneal cavity, approximately 3500 c.c. of clear light yellow fluid escaped. Delicate fibrous and fibrinous adhesions extended from the omentum, large bowel and stomach to the anterior abdominal wall. Almost the entire free surfaces of both liver and spleen were covered by similar fibrinous exudate and fibrous adhesions measuring 2 cm. in thickness. The liver extended 3 cm. beneath the costal margin.

On opening the chest, both pleural cavities were found to be completely obliterated by organizing fibrinous exudate about 2½ cm. thick. Similar adhesions were present between the pleural and pericardial surfaces.

The heart weighed 580 grams. The pericardial sac was completely obliterated by fibrous adhesions. The right auricle and ventricle, and the tricuspid and pulmonary valves were normal. The left auricular endocardium appeared diffusely thickened, and pearly gray in color. The mitral ring showed a minimal degree of stenosis and admitted the tips of two fingers with difficulty. Both mitral leaflets were moderately thickened. On the auricular surface of the free borders of the posterior leaflet were small verrucous structures measuring 1 to 2 mm. in diameter. They were friable and light red in color. Extending over the entire ventricular surface of this leaflet was a large vegetation 5 mm. thick. It was dark red, granular and fairly friable, and partly obliterated the pocket between the cusp and subjacent endocardium. It extended downward along the endocardium of the posterior wall of the left ventricle for a distance of 2 cm. The anterior mitral leaflet was sclerosed and contained a small calcified deposit in its depth. It was free of any vegetations that could be seen grossly. The chordae tendineae were slightly thicker and shorter than normal. The left ventricle was moderately hypertrophied; its wall was 14 mm. thick. The myocardium, aortic valve, supravalvular aorta and coronary arteries were normal.

The aorta was normal save for a few, light yellow, subintimal flecks in descending and abdominal portions.

The lungs were crepitant throughout. There were no areas of consolidation. A few small alveolar hemorrhages were noted in the right lower lobe.

The spleen weighed 510 grams. Its capsule was covered by loosely adherent fibrinous exudate 2½ cm. thick. The cut surface was deep red, with abundant pulp.

The stomach, intestines, pancreas and adrenals showed no noteworthy changes.

The liver weighed 1920 grams. Its free surface was covered by a fibrinous exudate similar to that covering the spleen. The cut surface was brownish red and the central veins were prominent. The gall bladder was normal.

There was a conspicuous inequality in the size of both kidneys; the left weighed 340 grams and the right weighed 120 grams. The capsule of the left stripped with

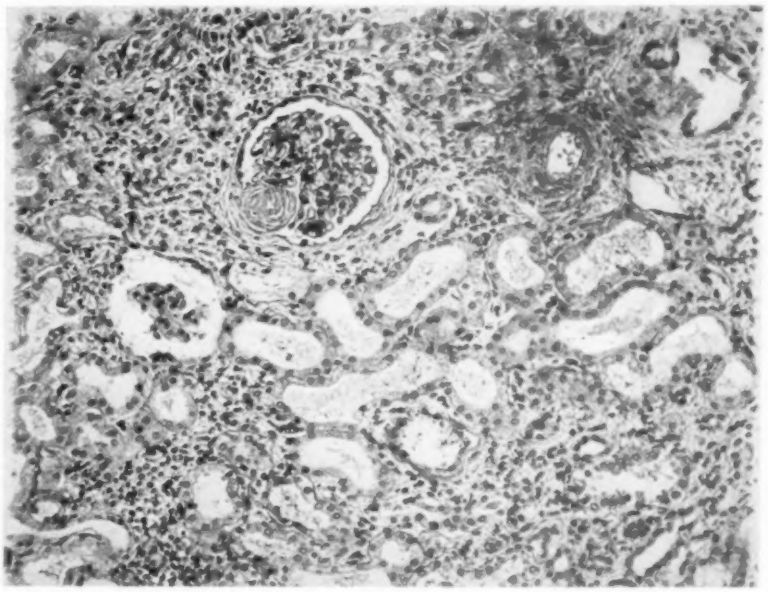

FIG. 4. Photomicrograph (low power magnification) of a section through right kidney showing healed focal lesion in the glomerulus like that seen in ordinary embolic glomerular nephritis.

ease, the surface was mottled, grayish yellow, and red because of small areas of congestion. The organ was softer than usual and on section the cortex was paler and wider than normal. The capsule of the right kidney stripped with some difficulty. The surface was pale reddish-gray and bore several linear cortical scars. The intervening surface between the scars was finely granular; the individual granules measured 1 mm. in diameter. On section, the cortex was markedly diminished in size and the cortico-medullary junction was indistinct. A slight degree of hydronephrosis with atrophy of the pyramids was noted but no ureteral obstruction could be found.

The bladder was normal except for a few small mucosal hemorrhages measuring 2 to 3 mm. in diameter.

The uterus, fallopian tubes and right ovary were normal. The left ovary contained a corpus hemorrhagicum measuring 1 cm. in diameter.

The peri-pancreatic lymph nodes were slightly enlarged, measuring 1 by ½ cm.

They were soft in consistency and the surface and cut section were pinkish gray in color. The remaining lymph nodes were normal.

The bone marrow of the vertebral bodies was normal. The remaining structures showed no significant changes. The brain was not examined.

Culture of the vegetations on the mitral valve revealed hemolytic streptococci.

Microscopic Examination: Heart: The posterior mitral leaflet was markedly and diffusely thickened by cellular granulation and fibrous tissue. There was extensive vascularization throughout its entire length and the vessels appeared as thick-walled arterioles in some regions but more often as young proliferating capillaries. There was an extensive proliferation of the histiocytes and a fairly dense focal infiltration of lymphocytes and polymorphonuclear leukocytes. There were many large hemosiderin-containing macrophages throughout the leaflet. The proximal three-fourths of the auricular aspect was lined by endothelium but the remainder as well as the entire ventricular aspect of the leaflet was the site of a homogeneous fibrinous vegetation which was continuous with the vegetation on the mural endocardium of the posterior wall of the left ventricle. The fibrinous vegetation appeared invaded by histiocytes and capillaries and showed very few polymorphonuclear leukocytes. There was fusion of the proximal portion of the ventricular aspect of the leaflet to the subjacent mural ventricular endocardium. This fusion appeared to be of firm fibrous nature and a similar union had occurred between many chordae tendineae and the ventricular surface of the leaflet as well as with the mural endocardium of the left ventricle behind the posterior mitral leaflet. There was no sclerosis or vascularization of the mitral ring. The endocardium of the left auricle showed no inflammatory changes. The anterior mitral leaflet showed alterations similar to that described in the posterior leaflet although on a smaller scale, including the fibrous cohesion of several chordae tendineae on the ventricular aspect. There were several large bacterial masses situated rather deeply in the leaflet though none were found on the fibrinous vegetation. In the leaflet itself polymorphonuclear leukocytes were fairly numerous.

The mural endocardium of the posterior left ventricular wall showed alterations similar to those found within the anterior and posterior leaflets; it did not extend beneath the elastic layers of the endocardium which were only slightly reduplicated. The endocardium was thickened to a degree which achieved a width of several mm. and the thickening was attributable to cellular granulation tissue well vascularized by thick-walled vessels and young capillaries on which was deposited a broad layer of homogeneous fibrin. Fused chordae tendineae could be very distinctly identified in this thickened endocardium.

The pericardium showed an extensive union with the epicardium by very vascular, loose, fairly cellular areolar tissue. There were thick-walled vessels in these fibrous adhesions as well as young capillaries. In a few places the adhesions between the serous membranes were of a homogeneous fibrinous character.

The myocardium beneath the mural endocarditis of the posterior left ventricular wall showed considerable fiber atrophy with interfibrillar fibrosis. Elsewhere the fibers showed a mild degree of nuclear and fiber hypertrophy. A few foci were encountered of sub-miliary size, consisting of a centrally placed capillary or arteriole plugged by bacterial masses with a surrounding zone of polymorphonuclear leukocytic infiltration and muscle necrosis. There were no Aschoff bodies or any structures even remotely resembling the latter. The larger and medium sized coronary arteries appeared normal. There was no perivascular fibrosis. There were a few small arteries and arterioles situated in the muscle subjacent to the mural vegetations in which definite intimal hypertrophy and medial fibrosis could be identified. A significant vascular alteration was found in thin-walled sinusoidal-like structures situated in the interfascicular connective tissue. These structures frequently con-

tained granular, pale, eosinophilic material, relatively acellular, surrounded by proliferating histiocytes and endothelial cells, practically occluding the lumen in many instances (figure 3).

Kidneys: Sections through the right kidney presented a uniform picture. The most striking alteration was that of extensive patchy tubular atrophy and interstitial fibrosis with condensation of glomeruli. In these patchy zones of atrophy, the most common glomerular lesion encountered was that of diffuse or partial hyalinization and atrophy, but within these areas, as well as in less altered portions of this kidney,

FIG. 5. Eleanor K., January 20, 1938. Eleanor K., May 18, 1938.

there were glomerular lesions of various other types. There were no glomeruli which appeared entirely normal. Many showed hyalinization of the so-called "focal embolic" type (figure 4), i.e., there was circumscribed hyalinization of a segment of the tuft with the remainder of the tuft showing only slight thickening of the basement membrane. These lesions appeared old and none showed evidence of recent necrosis. Other glomeruli showed a mild or moderate diffuse thickening of the capillary basement membrane with fusion of loops and simplification of the tuft. Many glomeruli showed synechiae between the tuft and the capsule. No crescents were seen but some glomeruli showed crescentic fibrosis. Many showed fibrous thickening of Bowman's capsule.

The tubules had disappeared in the large atrophic areas, elsewhere showed no alteration other than that of a focal calcification which involved collecting tubules chiefly. There was a moderate number of hyaline casts in the tubules. The interstitial tissue showed a diffuse fibrosis though the latter was more marked in the patchy zones of extreme atrophy. It was very densely infiltrated by lymphocytes and plasma cells.

The afferent glomerular arterioles and the interlobular arteries appeared entirely normal. There was, however, a severe focal lesion in the interlobar and arcuate arteries. A large number of these vessels showed partial or complete obliteration of the lumen by firm connective tissue in the intima which frequently showed capillarization. The internal elastic membrane was notably unaltered and the media and periarterial tissue appeared entirely normal in such lesions. This was, however, a focal process and more than half of the vessels of this size encountered in the sections appeared unaltered.

The mucous membrane of the pelvis and calyces showed a dense sub-epithelial infiltration of lymphocytes and plasma cells, and in some sections the calyx was full of pus.

The left or large kidney showed alterations of the glomeruli similar to that seen in the right. There was, however, a notable difference, in the absence of any extensive patchy atrophy or interstitial fibrosis. The process in this kidney was more diffuse and the interstitial scarring was less marked. The other difference appeared in the absence of any vascular lesion whatsoever, the arcuate and interlobar arteries in sections from this kidney appearing entirely normal. The pelvic mucous membrane showed the same inflammatory changes as noted in the right kidney.

Lungs: In all sections the pleural surfaces were thickened by fibrous exudate containing capillaries lined with thick cuboidal endothelial cells. The parenchyma showed a moderate degree of chronic passive congestion. One section contained several foci of organizing pneumonitis. Many of the smaller bronchi exhibited thickened fibrosed walls with foci of lymphocytes in their depths.

Spleen: The capsule was thickened in several areas by old fibrous connective tissue. The pulp was moderately congested and contained an excess of polymorphonuclear leukocytes. The follicular arterioles showed moderate intimal thickening of a hyaline nature.

Pancreas: The acinar and islet cells were normal. There was a moderate degree of diffuse inter- and intra-lobular fibrosis with atrophy of many of the glandular lobules. The thickened interlobular septa were infiltrated with moderate numbers of lymphocytes and fibroblasts. Scattered capillaries and venules exhibited partial or complete occlusion by hyaline masses, some of which were partially organized. The arteries were normal.

Liver: The capsule was normal but was covered by a very thin layer of delicate connective tissue strands. The central zone sinusoids were dilated with consequent atrophy of the surrounding polygonal cells. Many of the hepatic cells throughout the sections contained large lipoidal globules. The larger arteries exhibited slight intimal thickening by fibrous proliferation. The smaller vessels were normal.

Adrenal: The capsule was thickened by young fibrous connective tissue. A few of the capsular arterioles showed intimal proliferation, hyaline and fibrinoid degenation of their walls with consequent narrowing of the lumen. The remaining portions of the adrenal gland were normal.

Bone marrow: The bone marrow of the vertebral bodies showed hyperplasia of the cells of the granulocytic series.

The remaining organs showed no unusual changes.

Final Pathologic Diagnosis: Chronic polyserositis (pleuritis, pericarditis, perihepatitis, perisplenitis) with ascites; chronic passive congestion of the lungs and

liver; chronic active mitral and left ventricular mural endocarditis of the atypical verrucous type with superimposed acute bacterial (hemolytic streptococcus) endocarditis; chronic glomerular nephritis of the diffuse and focal embolic type; focal endarteritis obliterans of the right kidney with patchy ischemic atrophy; chronic bilateral pyelonephritis; chronic interstitial pancreatitis with capillary fibrinous thrombosis and lymphadenitis of the peri-pancreatic nodes.

Discussion

In 1924, Libman and Sacks [9] described what they considered a distinct clinical syndrome associated with characteristic mural and valvular atypical verrucous endocarditis. Two of the four patients originally described by these authors had lupus erythematosus. In 1932, Gross [10] reported seven cases of Libman-Sacks disease; cutaneous lesions were present in three. In 1935, Baehr, Klemperer and Schifrin [2] reported 23 cases of fatal lupus erythematosus with autopsy findings. Five of these had endocarditis of the atypical verrucous type. Keil quotes the late Dr. Louis Gross as having been of the opinion that from 30 to 50 per cent of the cases of lupus erythematosus demonstrate this endocardial lesion. It seems then that patients with lupus erythematosus may or may not have atypical verrucous endocarditis and conversely patients with this unusual type of endocarditis may or may not have lupus erythematosus. Our patient had both the cutaneous and endocardial lesions. The superimposed bacterial endocarditis reported here is rare but has been noted by other observers and occurs quite late in the course of the disease.

Studies of renal function have been reported in only a few of the cases that appear in the literature. Keith and Rowntree [11] found that renal function as tested by phenolsulphonephthalein excretion, by the level of nitrogenous bodies in the blood and by the ability to dilute and concentrate the urine was unimpaired as a rule. Rose and Goldberg [3] found that in two of their cases the function as judged by urea clearances was normal; neither of these two patients had azotemia. Nine of the 23 patients reported by Baehr, Klemperer and Schifrin had azotemia and showed fixation of specific gravity of the urine. It is interesting that our patient showed first a marked impairment in renal function; i.e., a fixed specific gravity, a urea clearance which was 13 per cent of normal and a blood urea content of 217 mg. per cent, and then regained her capacity to concentrate urine and to clear urea (75 per cent of normal), thereby reducing her blood urea to a normal level. Even more striking is the fact that uremia, which in this disease is usually terminal, was followed by remission. In the latter phase of the patient's illness the urea clearance was again seriously reduced, though the blood nonprotein nitrogen during the last week of life was only 38 mg. per cent. Albuminuria and hematuria persisted practically throughout the patient's course, even when she was symptom-free and apparently in remission. As is the rule in these cases, hypertension was absent. As one follows the course of lupus erythematosus from its onset, it becomes evident that the

degree of renal function impairment may vary from time to time and may not be unremittingly progressive. This may explain, in part, the wide variation in the reported results of kidney function tests in this disease.

It is noteworthy that the customary leukopenia was not observed in this case. In fact leukocytosis was present through the major part of the course, reaching a maximum of 56,200 white blood cells. At autopsy the bone marrow was found hyperplastic, largely because of an increase in the cells of the granulocytic series.

Baehr, Klemperer and Schifrin are of the impression that those patients with erythematous lupus who are photosensitive, develop this disease or an exacerbation immediately after exposure to sunlight. Keil [12] disagrees with this observation. The case here reported demonstrates that while the patient was unquestionably sensitive to sunlight, exposure to sun did not immediately precede the onset of her illness nor the later appearance of the cutaneous manifestations. The skin eruption appeared several months after the other symptoms began, during which period the patient had remained indoors.

At autopsy the kidneys showed both diffuse and focal glomerular nephritis. Baehr et al. described glomerular lesions in 18 of 23 cases. Rose and Pillsbury [6] found them in all of the five cases autopsied and Reifenstein et al.[7] reported glomerular nephritis in 9 of the 17 cases collected from the literature.

An unusual feature in our case was the marked inequality in the size of both kidneys, one being almost three times as large as the other. It is noteworthy that many arteries of the smaller kidney were occluded, partially or completely, by severe intimal fibrosis. The internal elastic membrane and the remaining layers of these vessels remained unaltered. Such changes were conspicuously absent in the larger kidney. The " wire loop " lesions emphasized by Baehr and his co-workers were not found in this case.

The smaller systemic arteries, arterioles, venules and capillaries were widely affected. In most instances the changes consisted of intimal proliferation and fibrosis, in some the walls showed degenerative changes and in many the lumen was narrowed or occluded by thrombus formation. Such alterations were noted to a greater extent in the heart and kidneys and to a smaller degree in the spleen, pancreas, liver and adrenals.

The morphological changes in the heart conformed closely to the descriptions of Libman and Sacks and Gross.

Summary

A case of lupus erythematosus with visceral involvement is reported. It is unusual in that so many of the multiple features of this disease were observed in one patient.

The clinical attributes consisted of photosensitivity, cutaneous eruption, alopecia, arthritis, pericarditis, endocarditis, petechiae, papilledema, pleuritis, pneumonitis, nephritis, transient uremia, splenomegaly, hepatomegaly,

ascites, peripheral edema, gastrointestinal disturbances, prolonged fever, anemia, leukocytosis, delirium, convulsions and coma.

The significant morphological changes consisted of atypical verrucous endocarditis (Libman-Sacks) with superimposed acute bacterial endocarditis, adhesive pericarditis, disseminated vascular lesions, polyserositis, focal and diffuse glomerular nephritis and interstitial pancreatitis.

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THE RESPIRATORY AND THE CIRCULATORY SYSTEM IN FEMALES WITH OVARIAN DYSFUNCTION *

By David Scherf, M.D., *New York, N. Y.*

Some women pass through the climacterium asymptomatically, whereas others have innumerable complaints. Frequently symptoms do not cause undue annoyance and may be elicited only by careful questioning. In other cases they are so tormenting that medical treatment, bed rest, and even hospitalization may become necessary.

Opinion varies in regard to the incidence of symptoms. Some estimate it as high as 75 per cent of all women [11, 12] while others report 91 per cent or even more.[30] The marked difference in the intensity and frequency of symptoms seems to depend upon constitutional and endocrine factors and the status of the vegetative nervous system. Furthermore, the social position of the patient may play a rôle. One meets patients with climacteric symptoms much more frequently in private than in institutional practice. In the private practice of a cardiologist 22 per cent of female patients seeking advice had complaints caused by the disturbance of the activity of the ovarian glands.

It has been known for years that an arthritis or a psychosis (involutional melancholia) may be associated with the climacterium, and substitution therapy with ovarian hormones has been recommended. But even the relation of these conditions to the activity of the ovarian glands occasionally has been questioned and even denied until recently.

With regard to the sensations produced by disturbances of the circulatory system, it is generally appreciated that "hot flashes" and palpitation are common findings during, and caused by, the menopause. But these symptoms and others, which are discussed later, are usually regarded mainly as the consequence of a "climacteric neurosis" rather than of an actual illness. More recent investigations seem to prove, however, that these patients are actually ill and not merely neurotic. They indicate that the practical importance of the circulatory disturbances in climacteric females has been greatly underestimated.

Symptoms and Signs

In a typical case the diagnosis is possible by merely obtaining the history from the patient. Most of the patients exhibit increased excitability and show an emotional instability and great nervousness. They weep readily and are greatly depressed. Others, however, enumerate their symptoms with great tranquillity.

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From the Department of Medicine, the New York Medical College, Flower and Fifth Avenue Hospitals.

In the foreground are the "hot flashes" which are found in approximately 62 per cent of the cases.[12] Some authors, however, note them so regularly that they hesitate to diagnose the climacterium unless this symptom is present. Sweating, vertigo and a splitting headache are common.

Palpitation, cardiac pain and dyspnea constitute a syndrome encountered very frequently in patients with an organic heart lesion; but the same triad is also found with equal regularity in the climacteric female. More exact inquiry, however, often adds many important details. The palpitation does not present the characteristic features noted in paroxysmal tachycardia or of palpitation associated with organic heart lesions. It comes without apparent cause, frequently at night, and lasts only a few minutes. The pain is felt in the region of the cardiac apex or in the left parasternal region in the second or third interspace. This area is frequently hypersensitive to pres-

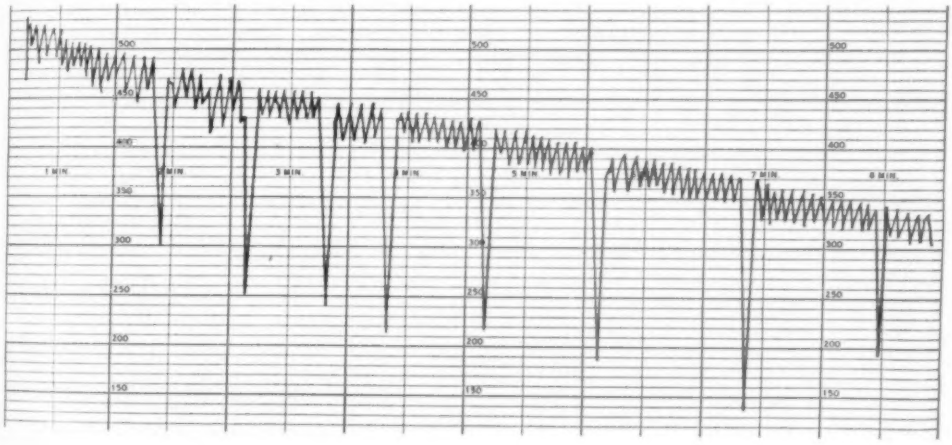

FIG. 1. Sighing respiration in a climacteric patient.

sure. Moreover, the pain may radiate "typically" to the left shoulder and down the left arm. It usually lasts but a few minutes, and is very similar to the pain found in myocarditis. Nitroglycerin may relieve.

The dyspnea of this group of patients presents features which are very suggestive of the correct diagnosis. It occurs independently of effort and may be present when the patient is resting quietly. Simple observation and careful questioning reveal that the dyspnea consists merely of single deep sighing respirations which recur at rather short intervals. Some relief of the oppression is thus afforded. Rarely is the patient aware of the true character of the respiratory disturbance, and therefore she mentions only the subjective feeling of dyspnea. When informed by the physician concerning the character of the breathing she recognizes immediately the sighing as such. This form of respiration is so typical that it readily permits the diagnosis.

Figure 1 shows the basal metabolism tracing of a 38 year old patient in the menopause, who complained of dyspnea and palpitation. The deep sighing respirations occurred once or twice every minute and are clearly visible. One will also notice that the deep respirations are not preceded by more superficial excursions, i.e., they do not have compensatory character.

Figure 2 shows the rather slow respiration of another patient, 54 years of age, who complained of dyspnea, palpitation, pain in the cardiac region and "hot flashes." In this instance as well the deep sighing occurred at least once every minute combined with an irregular and slow respiration. In both cases the disturbance of the respiration was very obvious during the examination. The basal metabolic rate in the two patients was —7.6 and —6.4 respectively. Both present quite typical instances of the two main varieties of the sighing respiration encountered in these patients.

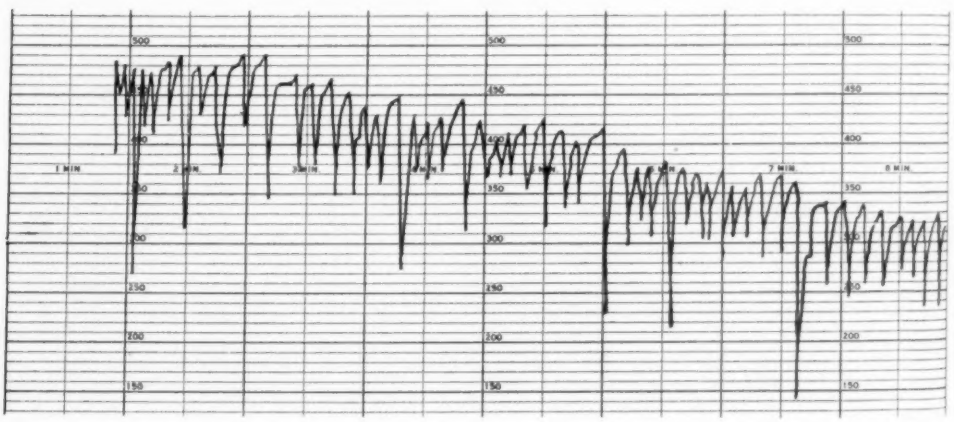

FIG. 2. Irregular sighing respiration in a climacteric patient.

The sighing disappears promptly after the administration of follicular hormone. If the treatment is discontinued it reappears occasionally until adequate treatment is again initiated.

Two thousand successive basal metabolism tracings were investigated regarding the described disturbance of respiration. It was found in 68 cases of which only two were males. Thirty-five of the females were older than 35 years and had symptoms and signs suggesting a disturbance of ovarian function. All but three of the other patients were registered under the diagnosis of hyper- or hypothyroidism, menstrual disturbance, endocrine imbalance, hypo-ovarism, fibroids, etc. In one of the two men with sighing respiration bilateral undescended testes were found.

In the past, when a patient complained very excitedly of pain, dyspnea and palpitation, when flashes of heat existed, and the woman had just arrived at or was in the menopausal age, and, moreover, the clinical examination revealed normal findings, the diagnosis "climacteric neurosis" or neurocirculatory asthenia was comprehensible.

Sometimes, however, in these patients a series of abnormal signs is found. Occasionally the heart is very excitable, decided pulsations are palpable over the entire precordium, the heart rate is increased, and a systolic murmur may be heard over the apex or the aorta. Tremor, dermography, sparkling eyes and other signs of hyperthyroidism are present. Sometimes a hypertension exists and values of 200 mm. Hg systolic and 100 diastolic may be observed for several years. When these signs, variously combined, were found, when the symptoms mentioned caused great distress and the electrocardiographic report suggested "evidence of myocardial lesion," then the diagnosis of angina pectoris, myocarditis, or coronary sclerosis was common. These patients were induced to lead a restricted life and were treated for years as cardiac patients with a doubtful prognosis until all symptoms and signs subsided.

The Electrocardiographic Findings

In some cases with definite climacteric disturbances it was striking that, during the time of the most pronounced symptomatology, marked alterations appeared in the electrocardiogram although they promptly disappeared on treatment with follicular hormone. Further investigations revealed that patients with ovarian hypofunction, without relation to the climacterium, may present the same electrocardiographic findings.

Frequently, but not always, a sinus tachycardia of 90–120 is found. The auriculoventricular conduction time is occasionally prolonged. The initial complex is not altered. Definite changes are found in the S–T segment and the T-wave.

The most typical finding is a depression of the S–T segment beneath the isoelectric line. This depression may be barely visible or very pronounced. It is usually present in every lead and, therefore, it is most marked in Lead II. Frequently it is accompanied by an alteration of the T-wave. The T-wave becomes lower and may disappear completely. Only rarely is it inverted. The changes of the T-wave are most pronounced in Leads I or III.

It is self-understood that only those changes of the S–T segment which are definitely abnormal have diagnostic value. Slight depression of the S–T segment occurs occasionally in the normal individual after exercise or during a sinus tachycardia. It is also important to rule out preceding treatment with digitalis, since these tracings may be similar in some respects to those of patients who were previously digitalized. It may be emphasized, however, that the slow descent of the S–T segment combined with the steep rise to the T-wave, so characteristic of the digitalis tracing,[31] is usually absent from these tracings.

Case 1. This 46 year old patient had suffered from substernal pain for several weeks. During the last week she frequently felt dull pain of variable intensity behind the sternum. The patient also complained of dyspnea and palpitation, independent of

effort. Swelling of the ankles was occasionally noted. Three years previously a panhysterectomy had been performed. The blood pressure was 135/65 mm. Hg. The examination of the heart revealed normal physical findings, except for slight hyperexcitability. There was also a slight tremor; the basal metabolic rate was plus 35 per cent.

The electrocardiogram (figure 3*a*) shows a sinus tachycardia with a rate of 115. The S–T segment in Lead II is slightly depressed, and there is no T-wave. The patient had never received digitalis. Two thousand units of follicular hormone were injected daily. No other medication save a sedative was given. The electrocardiogram, recorded one week later (figure 3*b*), shows a rate of 95; the depression of the S–T, most pronounced in Lead II has disappeared, the T in II is normal and positive, and in Lead III the T-wave is less negative than before the treatment. The pain and other symptoms had disappeared in the interim. The blood pressure fell to 112/75 mm. Hg. The basal metabolism was only 11 per cent plus.

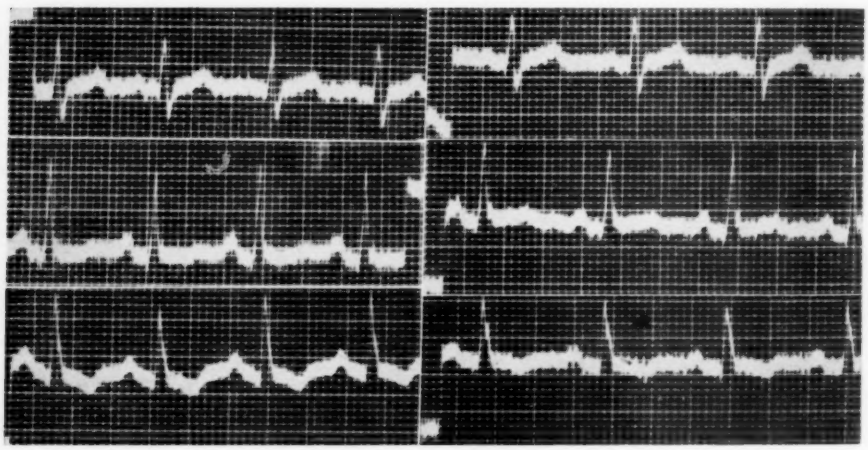

FIG. 3. Electrocardiogram before and after estrogen treatment in a climacteric patient.

Case 2. This patient was 59 years of age and complained of "flushes," pain in the precordium, palpitation and dyspnea. A year previously a panhysterectomy had been performed and the symptoms developed slowly one month ago. The clinical examination revealed a hyperexcitable heart with normal physical findings.

Figure 4*a* shows a regular sinus rhythm with a conduction time of 0.22 second. The initial complexes are normal. The S–T segment in Leads I and II are definitely depressed, the T-waves are almost invisible in all limb leads. In the right arm—precordium chest lead the T-wave is inverted, in the right arm—apex chest lead there is a bifid T. The patient was treated with six intramuscular injections, each containing 10,000 units of follicular hormone. The injections were given twice weekly. No other therapy was employed.

Figure 4*b* shows the electrocardiogram after three weeks' treatment. The conduction time is normal (0.18 second); the S–T segment and T-waves are also normal in the limb leads as well as in the chest leads. The patient noticed a marked improvement and became symptom free.

Case 3. Figure 5 shows very typical and advanced changes. The patient was 48 years old and she had not menstruated for four months. She complained of pains in the region of the heart, hot flashes, palpitation and marked excitability. The blood pressure varied continuously between 180/60 and 220/75 mm. Hg. The heart was

very active, with strong precordial pulsations; however, it was not enlarged. Basal metabolism was + 70 per cent.

The electrocardiogram (figure 5) shows a sinus tachycardia with 130 beats per minute and a deep depression of the S–T segment, especially in Lead II. The patient had never received digitalis. Treatment with follicular hormone (10,000 units intra-

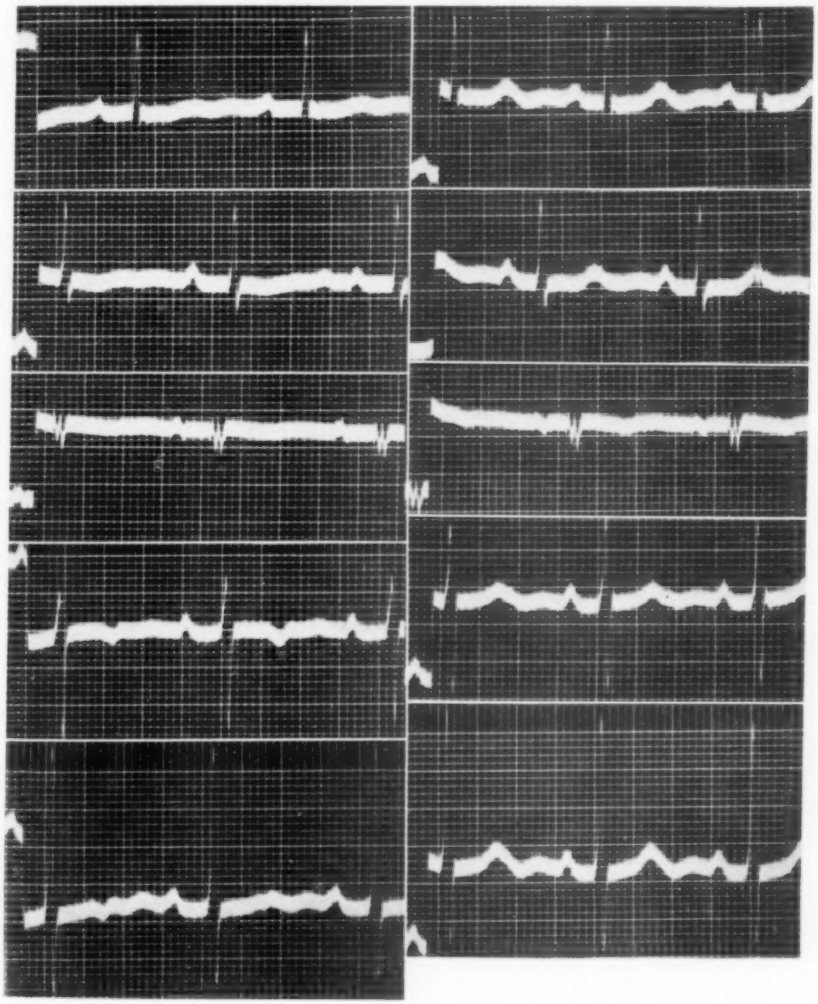

FIG. 4. Prolonged conduction time and abnormal T-waves in a climacteric patient, a normal electrocardiogram appearing after 3 weeks' treatment.

muscularly, twice a week) was instituted; this abolished all symptoms within five weeks.

Case 4. This 52 year old patient suffered from palpitation, pain in the precordium while at rest, and a feeling of anxiety. Menstruation was still undisturbed. The blood pressure varied on different occasions between 180/80 and 200/120 mm. Hg, within short intervals of time. The heart was normal in size and form, but hyperexcitable.

The electrocardiogram again shows typical changes (figure 6*a*). There is again a sinus tachycardia with a rate of 97. The initial complex shows a left axis deviation without widening or splitting. The S–T segment is again markedly depressed. The T-wave is low, especially in Lead II. Within 14 days following the treatment with four intramuscular injections, each containing 50,000 units of follicular hormone, the electrocardiogram was practically normal (figure 6*b*).

No strict parallelism exists between the extent of alterations in the electrocardiogram and the complaints. One may see patients with marked flushing and palpitation but a normal electrocardiogram; on the other hand, if the electrocardiogram displays the abnormalities mentioned above these symptoms are never absent. In patients who complain of pain in the cardiac region the electrocardiogram is usually altered.

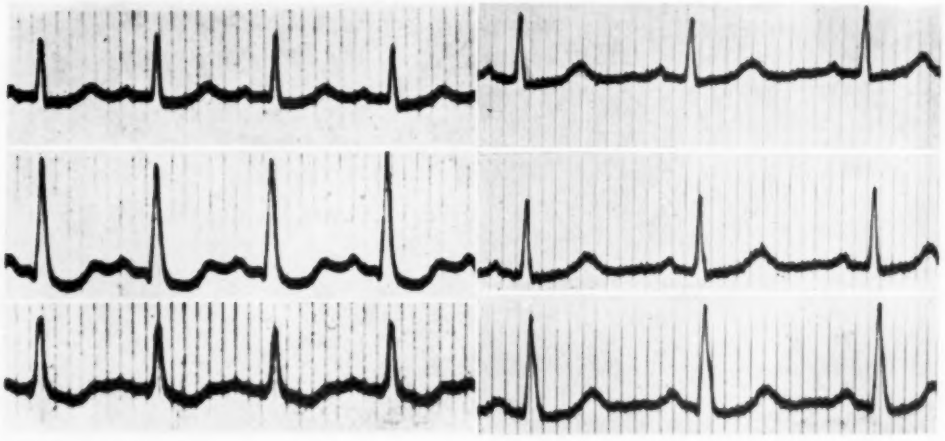

FIG. 5. Marked changes of the S–T segment in a climacteric patient with hypertension, and the changes after treatment. In the tracing on the right the order of leads is I, III, II.

The alterations in the electrocardiogram may be recorded not only in patients in the natural or artificial climacterium (after irradiation or operation), but they may be also seen in young females with ovarian hypofunction.[24] In these patients hypogenitalism usually exists. The menstruation is painful and of short duration, and the menses may disappear for several months. Acrocyanosis, with cold, blue, perspiring fingers, is a frequent finding. The heart may show hyperactivity, but is never enlarged. Tachycardia and a systolic murmur are frequent, and occasionally an elevation of temperature is found, especially before menstruation. If a depressed S–T segment and inverted T-waves, i.e., signs of myocardial damage, are discovered in the electrocardiogram of these cases, the mistaken diagnosis of a myocarditis, sometimes even endocarditis, is commonly made. Some of these patients have been confined to bed for months.

The changes in the electrocardiogram are independent of the signs of hyperthyroidism. This deserves emphasis because in some places hyperthyroidism very

frequently accompanies the menopause.[17] In other regions this combination is much rarer and patients with signs of hypothyroidism are more frequently encountered. Occasionally, mixed forms with signs of hyper- and hypofunction of the thyroid are seen. The changes in the electrocardiogram described above may appear in both types of patients. Naturally they are more frequent in patients with hyperthyroidism, but they disappear after adequate treatment with follicular hormone within a short time whereas the signs of hyperthyroidism still persist. The hyperthyroidism is only a coincidental symptom of the menopausal syndrome. On the other hand, these electrocardiographic changes are not observed in patients with pure hyperthyroidism. The latter group has normal electrocardiograms, sometimes with T-waves of unusual height. Occasionally abnormal S–T segments and T-waves are found, but only in very toxic cases.

The alterations of the electrocardiogram are also not the result of the hypertension. One frequently finds the same changes in patients with a normal blood pressure, especially in younger individuals. In patients with hypertension, too, the

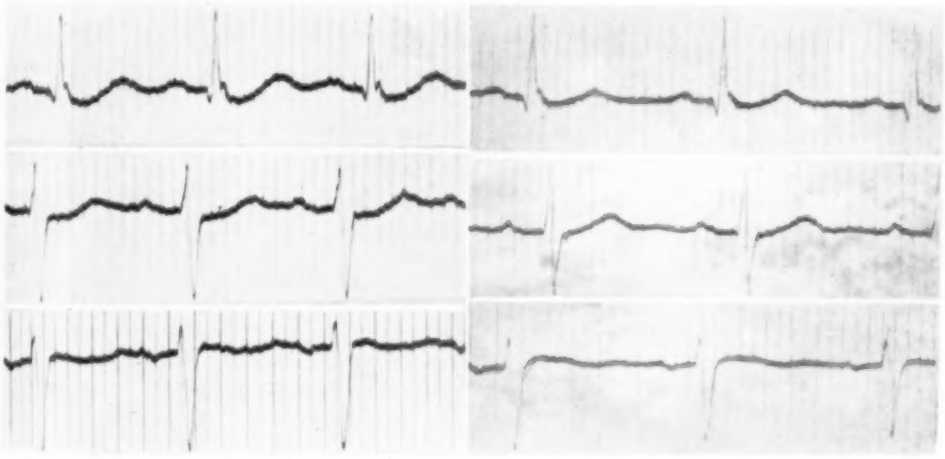

FIG. 6. Electrocardiogram before and after the administration of estrogenic hormone.

electrocardiogram may become normal after treatment with follicular hormone before the blood pressure falls. The electrocardiographic changes may also disappear in climacteric patients with an essential hypertension after the administration of follicular hormone although the blood pressure remains at the same level. Moreover, the changes in the electrocardiogram produced by a hypertension are quite different from those described in this paper, since in hypertension one commonly finds a levocardiogram which, in the later stages, shows a depressed S–T and T in Lead I and an elevated S–T and T in Lead III. But in the group we are describing, a co-existing hypertension may aggravate the alterations.

The relation between the electrocardiographic changes and the ovarian dysfunction is proved by the fact that the alterations of the final deflection and of the conduction time disappear after a short treatment with follicular hormone.

After interruption of treatment the alterations of the electrocardiogram may reappear after weeks or months. If follicular hormone therapy is again instituted the electrocardiogram becomes normal.

The changes described were observed in 38 cases. Some were treated under the diagnosis of angina pectoris, myocarditis or coronary sclerosis for many months;

the electrocardiogram remained unchanged. Administration of follicular hormone abolished every alteration in one to three weeks.

Since objective signs permitting the diagnosis of an ovarian dysfunction are not available, it is impossible to determine the percentage of these patients in which these electrocardiographic changes appear. They are found only in a minority of the climacteric patients and are by no means a fixed characteristic of this event. As in climacteric hypertension and other climacteric phenomena, a certain "status of the endocrine glands" is necessary for their appearance.

Hypertension and Other Circulatory Disturbances in Patients with Ovarian Dysfunction

Until recently the existence of a climacteric hypertension was denied by very competent observers.[7, 18] Others assume that about 40 to 50 per cent of climacteric females show an elevated blood pressure,[17] and some believe that high blood pressure in the climacterium is a physiological phenomenon. The literature on these questions is extremely contradictory and reflects marked differences of opinion. Since many studies were reported by excellent clinicians, one must assume that the number of cases showing hypertension in the natural or artificial climacterium varies in different countries. Personal experience confirms this assumption, since a change of sphere of activity permitted the writer to observe a difference in the frequency of hypertension in patients with the described syndrome.

If hyperthyroidism is not very marked, the systolic and diastolic blood pressures are increased. Values over 200 systolic and over 100 diastolic are not unusual. In patients with a hypertension of other genesis the blood pressure values may rise to still higher levels in the climacterium. The rapid and frequent fluctuation of the blood pressure is very characteristic. Patients with very outspoken symptoms and signs and with normal blood pressures are especially common among younger females. Here the extirpation of both ovaries and the uterus occasionally does not create any symptom [33] and the blood pressure frequently remains normal.

In the group of patients whose blood pressure increases, a marked dilatation of the heart may be found at times. At times an attack of cardiac asthma or pulmonary edema may appear even before the heart undergoes much enlargement.

Case 5. This 45 year old patient, the mother of two children, had always been well. Menopause occurred two years previously. A few months later hot flashes appeared. The physical examination was negative. In the following month the blood pressure gradually increased to 160/80 and 200/95 mm. Hg. Extrasystoles frequently occurred, and signs of hyperthyroidism appeared. The electrocardiogram showed the characteristic depression of the S–T segment, mainly in Lead II. On two occasions, once after a heavy meal and once after great excitement, attacks of pulmonary edema appeared, and injection of morphine and digitalization were necessary. Treatment with follicular hormone quickly abolished all symptoms and signs. Subsequently the blood pressure never exceeded 145/70 mm. Hg, although the signs of slight hyperthyroidism remained. The attacks of pulmonary edema did not recur in the next two years, despite the fact that the patient did not receive any treatment except follicular hormone. The electrocardiogram was normal thereafter.

Two other patients had had attacks of paroxysmal fibrillation in the climacterium only during the period of flushes, palpitation and heart pain.

Case 6. This patient, at present 62 years of age, had always been healthy; her menopause occurred 14 years ago. Six years later flushes, palpitation and hyperexcitability appeared. The blood pressure reached 200/110, but fluctuated markedly. For two years, at the height of these symptoms and signs, seven attacks of auricular fibrillation occurred, lasting one to four and one-half hours. Treatment with sedatives and ovarian hormone abolished all the complaints. The heart has remained normal and no further attacks of fibrillation have appeared.

In cases of this kind it will frequently be difficult, or even impossible, to rule out another cardiac lesion, for example coronary sclerosis; however, the possibility of a disturbance connected with the climacterium should always be considered and adequate treatment should be instituted.

Treatment with Estrogenic Hormone and the Electrocardiogram

In every case the administration of follicular hormone was followed by a very rapid relief of symptoms and a return of the electrocardiogram to normal, if sufficient doses were administered. The tachycardia which was frequently present disappeared, the depression of the S–T segment and the abnormality of the T-waves changed gradually to terminal deflections of normal appearance. In some cases the electrocardiographic changes have vanished within eight days after the administration of as little as 1000–2000 international units daily. In other cases injections of 10,000 or 50,000 units two to three times weekly for three to four weeks were necessary to produce an improvement. The doses necessary naturally differed in each case. In some younger patients the injection of gonadotropic hormone seemed preferable. At the beginning, suppositories or injections were usually given, depending on the severity of the case, but later on, after the effect was established, oral administration was usually sufficient. In the females who were still menstruating the best results were obtained when the follicular hormone was given during the first 10 to 15 days after menstruation. After the menopause the patients were always informed that bleeding might again occur during the treatment.

The treatment in younger patients and in patients with disturbances of the menstruation was never undertaken without consultation with a gynecologist. If fibroids were present the follicular hormone was employed very cautiously. When bleeding occurred during treatment, in a patient after the menopause, the patient was also sent to a gynecologist. The value of this procedure was illustrated by one case, a 56 year old patient, who developed slight metrorrhagia after the use of 20 suppositories each containing 5000 units of follicular hormone. The gynecologist found a uterine carcinoma, which was operated upon. There is no reason for presuming that the treatment itself may cause a carcinoma.[14]

Patients with Organic Heart Lesions and the Climacteric

If the disturbances accompanying the climacterium have such a profound influence on the heart of the healthy female, it is easy to understand their importance for patients who already harbor an organic heart lesion. It has been known for a long time that an organic valvular lesion or a hypertension may be fully compensated, and even asymptomatic, for years and decades until the mid-forties are reached; then quite suddenly and unexpectedly decompensation sets in.[17] The heart dilates quickly, cardiac asthma, pulmonary edema and peripheral congestion appear. This event is not rare and can be avoided. The estrogenic function of every cardiac patient should be continuously controlled, especially if the patient is in the age period during which climacteric disturbances occur. Prophylactic treatment with follicular hormone, if instituted early, might save many lives.

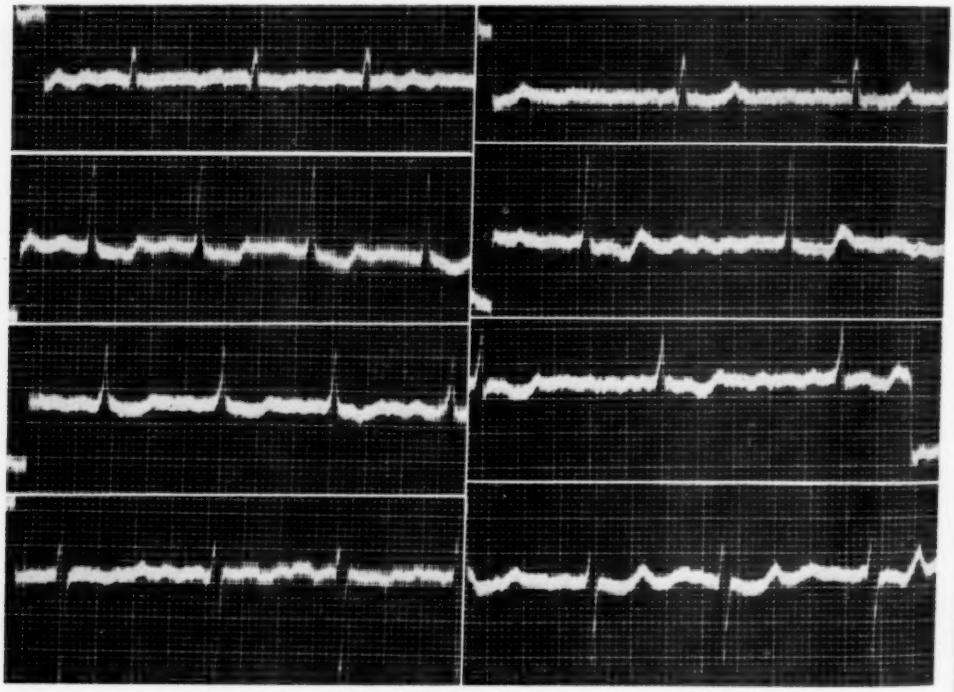

Fig. 7. Case of mitral stenosis and auricular fibrillation in the climacterium before and after treatment.

Case 7. Figure 7 was transcribed from a patient with mitral stenosis of 40 years' duration. The patient had polyarthritis at the age of eight. Five years previously the uterus was extirpated because of fibroids. Shortly afterward she began to complain of breathlessness and palpitation. During the last year the patient suffered from pain of a "crushing" and non-radiating character; this was felt behind the sternum and recurred three to four times an hour both day and night.

On admission mitral stenosis without congestive failure was found. The basal metabolism was —10 per cent, and the blood pressure was 110/80 mm. Hg. The electrocardiogram revealed auricular fibrillation (figure 7*a*) with a depressed S–T segment in Leads II and III. The T-waves are almost invisible in all leads. No axis deviation was present. The patient was treated with 1½ gr. of digitalis, twice daily. Three weeks later the electrocardiogram shows (figure 7*b*) a slower heart rate; the depression of the S–T segment is still present (digitalis?), but the T-waves are much higher, especially in Leads I, II and the chest lead (left leg to the apex).

Case 8. A 40 year old patient, with an insufficiency of the aortic valve and a mitral stenosis, complained of palpitation, oppression, dizziness and dyspnea only on exertion. Her menstruation was irregular and lasted only one day. The physical findings were those of a rheumatic mitral and aortic lesion without congestive heart failure. The electrocardiogram (figure 8*a*) showed a sinus tachycardia with a conduction time of 0.21 second. The S–T segment is depressed in all leads, but mostly in Lead II. There are no T-waves.

After the daily administration, for 20 days, of suppositories containing 5000 units follicular hormone, the heart rate is slower, the P–R distance is shortened to 0.18 second (figure 8*b*), the S–T segment and T-wave are normal.

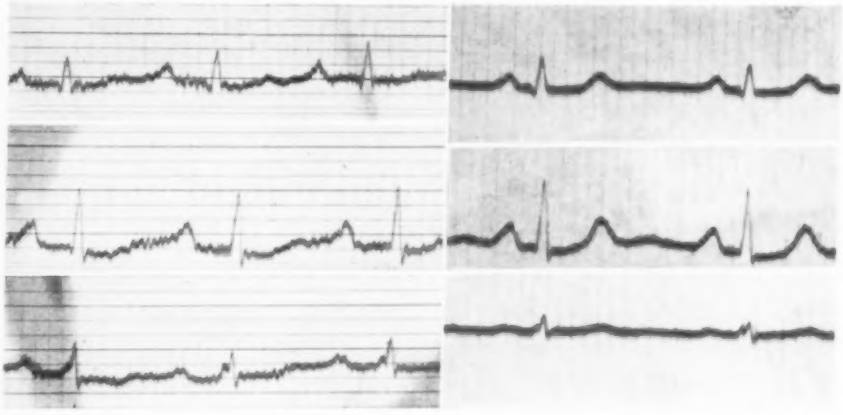

FIG. 8. Case of aortic and mitral lesion before and after treatment; note the prolonged P–R interval and the abnormal T-waves before treatment.

In patients with an essential hypertension the timely administration of follicular hormone may cause an astonishing improvement of the symptoms even without a change of the blood pressure.[24]

MYOMA HEART

In this connection passing allusion may be made to the question of the existence of a so-called "myoma heart." For more than 50 years cardiac changes have been described in patients with uterine fibroids.[2, 3, 19, 28] The relevant literature is enormous. Time and again changes in the hearts of patients with uterine myomata have been denied. The circulatory disturbances are ascribed frequently to the mechanical effect of a large tumor, to the accompanying anemia, or to the formation of an unknown substance by

the tumor. These arguments were disputed by others who found evidences of cardiac damage without anemia, without a large tumor, etc. Considerable confusion has been caused by premature conclusions from a small number of cases or even from a single case. The fact that the anatomical examination of the heart did not reveal any abnormal findings [16] does not prove very much, since the histological method is completely inadequate for demonstrating many other types of myocardial damage. A heart damaged by toxins or a heart weakened by chemical poisons frequently fails to exhibit any changes in the myocardium which can be histologically diagnosed. In recent years, however, most pathologists, gynecologists, and cardiologists deny the existence of a "myoma heart," although the possibility of toxic or hormonal effect from the fibroids upon the heart is mentioned. Ovarian dysfunction has been both assumed [28] and denied.[8]

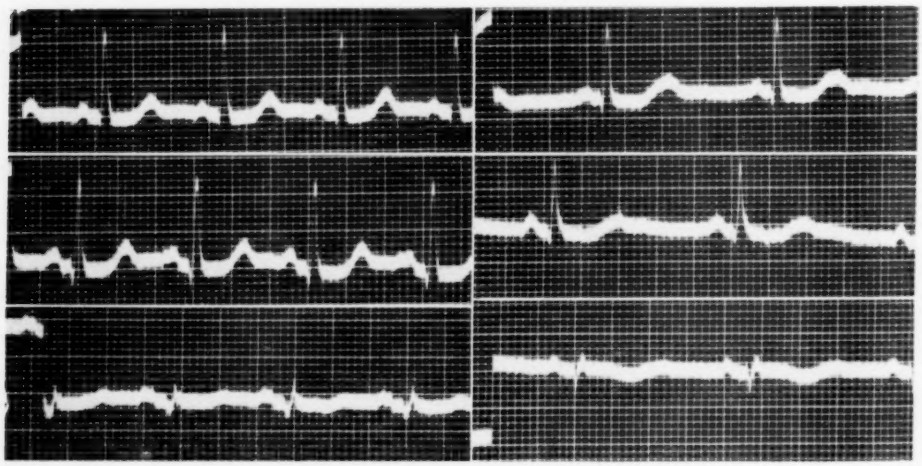

FIG. 9. Electrocardiogram of two cases of fibroids.

In patients with uterine fibroids we observed electrocardiograms which are very similar to those found in females with hypo-ovarism. Here also the depression of the S–T segment below the isoelectric line, especially in Lead II, is the most constant finding. Figure 9 shows electrocardiograms of two patients with uterine fibroids (43 and 57 years of age) in which the depression of the S–T segment is clearly visible. In more advanced cases alterations of the T-waves also appear.

Fetter and Schnabel described abnormal electrocardiograms in patients with fibroids. They ascribed the changes in their cases to the abnormal position of the diaphragm, caused by the large tumors. A study of their paper reveals, however, that the observed alterations in the electrocardiogram are very similar to those described in this paper as a consequence of a dysfunction of the ovaries.

Further studies now in progress should answer the question as to whether the heart damage, which in our opinion occurs undoubtedly in patients with fibroids even without anemia and with small tumors, may be ascribed to the same mechanism.

Most fibroids cause symptoms in the climacterium and in the preclimacteric age. Moreover, an interrelation between uterus and ovaries seems to be established, among other things, by the fact that extirpation of the uterus without any damage to the ovaries or their blood supply may cause "climacteric" symptoms. Accordingly there seemed to be some basis for the opinion that in these cases we are dealing with the same disturbance.

We may assume that in a myoma heart the disturbance is caused in a way which is very similar to that discussed in this study. The electrocardiographic changes, which Fetter and Schnabel explained by a mechanical displacement of the heart by the tumor, actually are quite different from those which may be found with abnormal elevation of the diaphragm.

Discussion

For several years the symptoms and signs of the climacterium have been attributed to an ovarian dysfunction. They are not ascribed to the menopause itself, despite the fact that frequently they coincide in time. The term, "circulatory disturbances of the menopause," though in vogue, causes errors and misunderstanding. We found the same disturbances in young females with hypo (dys-?) function of the ovaries. They may be observed years before the menopause and even 10 to 15 years following it.

In analyzing the underlying disturbances, discussion may be confined to the alterations of the electrocardiogram, since they are easily and objectively controlled. These electrocardiographic changes could be evoked by a lesion of the heart muscle itself or by an involvement of the coronary vessels and a secondary change in the condition of the myocardium.

As yet no proof of a primary tissue lesion has been obtained in these patients. In this connection the interesting changes in the content of serum calcium in conditions of hyper- or hypofunction of the female sex glands may be mentioned.[22, 35] The electrocardiograms described, however, do not show the changes of the R–T interval which are typical for hypocalcemia.

A number of observations and facts speak in favor of the responsibility of the narrowing of the smaller coronary arteries; this, in turn, may be caused by an involvement of the vascular wall or by an abnormal reaction of the vessels to substances or hormones in the circulating blood; abnormal quantities of these hormones might also be present.

(1) Rapid changes of the electrocardiogram are not infrequently observed. The form of the T-waves or of the S–T segment may undergo alterations within a few hours. Observations of this kind are not easily explained by a structural myocardial lesion. Moreover, these rapid changes are common in disturbances of the blood supply to the heart caused by syphilitic or sclerotic involvement of the coronary arteries. (2) Other vascular phenomena are frequently observed in such patients. For many years the picture of acrocyanosis in patients with hypogenitalism and dysfunction of the ovaries has been a familiar one; this is also successfully treated with follicular hormone. It is also known that numbness of the extremities, for-

mication, sensations of heat, local congestion, cold hands and feet, paresthesia of the arms and legs, and finally the changes in the systolic and diastolic blood pressure, are vascular phenomena which are amenable to hormonal treatment. (3) Anginal pain with typical radiation may appear. (4) Retinal vascular changes in climacteric females with hypertension have been observed; they disappeared after the administration of follicular hormone.[6, 6a] (5) Vasodilators (nitroglycerin, theobromine, papaverine) have an excellent effect in patients of this kind. This has been known for many years and was discovered purely empirically. (6) Many investigators have found that female sex hormone has a vasodilating effect. Its therapeutic use in the treatment of organic peripheral vascular diseases has been frequently recommended.[21, 26, 27]

Nevertheless, no proof has been obtained up to the present time for the validity of the above explanation although it seems to possess more probability than the presence of a primary tissue lesion.

The finer mechanism and primary cause of the disturbance may be explained by the imbalance of the endocrine glands resulting from the interruption of the normal function of the ovaries. The inhibitory action of the follicular hormone on the hypophysis ceases, and therefore an increased formation or unopposed action of various hypophyseal hormones results. The increased formation of the thyrotropic and adrenotropic hormones has been proved. Some observers also assume that a hypersecretion of vasopressin occurs.[25, 34] It is possible that these hormones cause hyperexcitability and hypercontractility of the heart and an increase of the blood pressure; this augments the work of the heart muscle and increases its need for oxygen. This action, in conjunction with even a slight narrowing of the vessels, may cause a relatively inadequate blood supply to the hyperactive heart, may cause pain, and the alterations in the electrocardiogram described.

Whatever the finer mechanism of the damage to the heart may be, it is clear that it is not a failure to form follicular hormone but the abnormal action of the other glands which is responsible for the signs and symptoms. Vasomotor disturbances, such as flushes, are frequently observed at a time when satisfactory ovarian function is still present.[1, 14, 29] Observations of this nature and the fact that "climacteric disturbances" may appear after hysterectomy without injury to the ovaries represent the basis of the postulation that an unknown hormone is formed in the uterus.[14]

There is considerable evidence to support the assumption that the disturbances described above are not confined only to the heart muscle and the circulatory system. Not rarely, by careful investigation and examination, abnormal conditions are found in other organs. Most of them were already known before the changes in the heart were appreciated. The climacteric arthralgia[10] and mental disturbances have already been mentioned. Albuminuria is not rarely observed,[4] and frequently pitting edema appears on the upper or lower extremities and occasionally even on the face. These phenomena, in conjunction with the symptoms and signs described, are frequently the occasion for unnecessary digitalis therapy, since congestive heart failure is mistakenly diagnosed. The deep sighing respiration provocative of a feeling of

oppression and breathlessness, which disappears like all other related phenomena after the administration of follicular hormone, points to the existence of an abnormal situation in the respiratory centers. Changes in gastric acidity,[9] obstipation or diarrhea have been observed. It seems permissible to assume that many, if not all, tissues occasionally may be involved. Unfortunately for most of them no method of examination as sensitive and as exact as the electrocardiogram for the heart is available.

This deep sighing has been described by P. D. White as a symptom of neurocirculatory asthenia.

A great deal has also been written about the male climacteric. Recently its existence has been denied on the basis of theoretical arguments. It is true that symptoms and signs as pronounced as in climacteric females are never observed in males, but one occasionally meets patients with oppression or pain and pressure in the heart region without any sexual disturbance and without any evidence of an organic cardiac lesion for many years, and usually a diagnosis of cardiac neurosis is made. In these patients one may occasionally find a slight, but definitely abnormal depression of the S–T segment. Proof that the same or a similar disturbance, but one of lesser severity, exists here, could not be obtained, because no opportunity has as yet been afforded in these patients to use hormonal treatment with substances of the same activity as those available for treatment of the female climacteric.

Summary

In patients with hypofunction (dysfunction) of the ovaries prolonged conduction time and abnormal sinal deflections may be found in the electrocardiogram. The alteration of the sinal deflection is usually most pronounced in Lead II.

These findings disappear after the administration of follicular hormone.

A disturbance of the respiration, characteristic of these patients, is described.

Similar changes may be found in patients with uterine fibroids.

The finer mechanism of the described lesions and their clinical importance are discussed.

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TRICHINIASIS: CLINICAL CONSIDERATIONS *

By Robert E. Kaufman, M.D., *New York, N. Y.*

Trichiniasis is an acute febrile illness caused by a nematode, *Trichinella spiralis* ["little spiral hair"]. This disease is the only metazoan infestation in humans which is regularly accompanied by fever. It is a much more common disease than is generally recognized, having been found in from 10 to 25 per cent of autopsies in which trichinae were specifically searched for.[1, 2, 3, 4, 5] As summarized by Hall[6]: "Nine groups of workers from 24 hospitals in 11 widely scattered cities in the United States found over 12 per cent of cadavers with evidence of trichinous infection. Trichinosis is a major public health problem." Scheifley[7] feels that the evidence indicates an incidence among adults in the United States of about 20 per cent. It is clear that Magath[8] was not exaggerating when he said that "in the United States 10 to 20 per cent of adults have acquired trichinosis, although most of them have never had symptoms suggestive of trichinosis." Hall and Collins[9] clearly state the gravity of the situation with the conservative estimate that "there are probably several million persons in the United States who are infested with trichinae, among whom are possibly several hundred thousands who have had clinical trichinosis never diagnosed as such, and there are possibly several thousand deaths annually from this cause."

Season and sex have no appreciable influence on the incidence of the disease. Age plays a rôle only because children under 3 or 4 rarely eat foods containing trichinae. All ages are susceptible, however, and in animal experimentation it is easier to infect the young than adults. An attack of trichiniasis apparently does not confer a permanent immunity, as patients are occasionally seen who have had two attacks (such as case 5 in this paper). The frequency of a recognized second or third infestation would undoubtedly be greater if the clinical diagnosis were made more often and if patients always knew or remembered that they had had trichiniasis years before.

Man is infected by eating meat harboring trichinae. When flesh containing the larvae is ingested, the capsules of the cysts are dissolved by the digestive juices and the larvae penetrate into the intestinal mucosa. Here the male and the female sexual forms develop and copulate about 40 hours after the meat is eaten. The pregnant females, still residing in the intestinal mucosa, lay their eggs—about 1,000 embryos by each female. The newly born trichinae enter the intestinal lymphatics about the fifth day, and are disseminated throughout the body via the blood stream. The predominant localization of the larvae is in the voluntary muscles, where they

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From the Medical and Pediatric Services of the Lenox Hill Hospital, New York City.

are first found about the sixth to eighth day after ingestion and where they eventually become encapsulated in an ovoid capsule, at first translucent but later infiltrated with lime salts.

The first complete description of the *Trichinella spiralis* was published in 1835 by Owen, after Hilton had discovered the capsule and Paget the enclosed worm. Twenty-five years later the scene shifts from London to Dresden, where Zenker demonstrated the danger of this parasite by finding it at autopsy in the muscles of a patient supposed to have died of typhoid fever. He discovered that the patient had eaten meat from a certain pig and that many others who had partaken of the same meat were ill. The final link in this brilliant clinicopathological demonstration was the finding of trichinae in the muscles of that hog. For a number of years after this, most of the work on the disease was done in Germany, where there were many cases and some very large outbreaks. During the past 25 years almost all the advances—clinical, experimental, and immunological—have been made in the United States. The history of the early work on the parasite, its development in the infested organism, and the pathological changes in the muscles are so admirably described by Sobel [10] that no further mention of these aspects will be made in this paper.

The trichina has been found in many species and can be experimentally transmitted to a great many others. The most common natural hosts are the rat and the pig, which serve as a large reservoir keeping the species from becoming extinct. Man is infected in almost all cases by eating pork products, such as undercooked ham and pork, salami, liverwurst, bratwurst, pig's feet, smoked and pickled ham and pork, sausages ("hot dogs"), summer sausage (cervelat), and hamburgers, which frequently contain ground pork scraps. There has been an outbreak in this country from bear meat [11] and one in Germany from polar bear meat.[12] In some countries the disease is probably transmitted to humans by improperly cooked dog meat.[13]

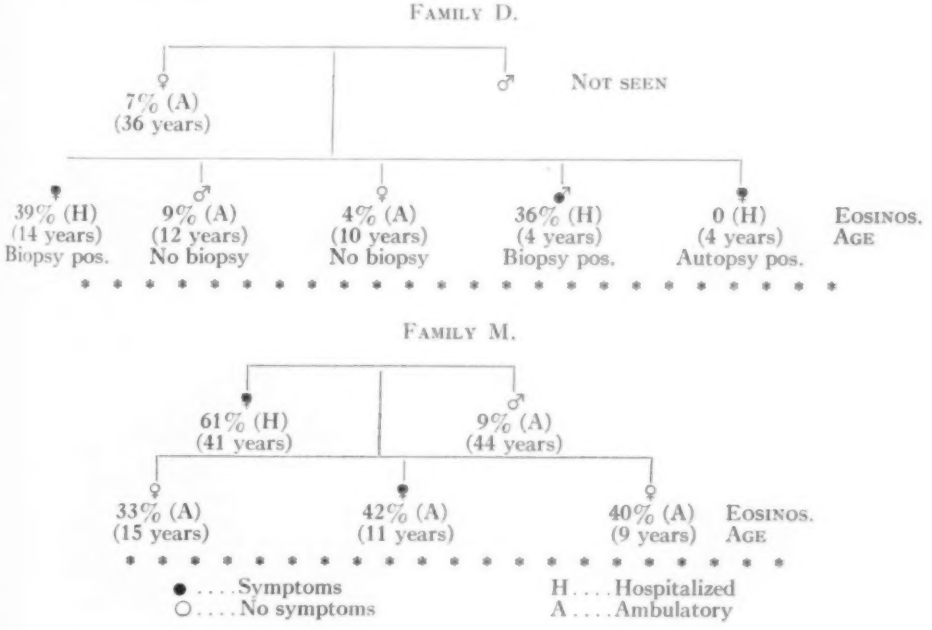
Prevention of trichiniasis is relatively easy compared to that of many other diseases of man, since the only measure necessary in the vast majority of cases is the thorough cooking of all pork and products containing pork. This, incidentally, will also prevent infestation with *Taenia solium*, the pork tapeworm. The trichinae, with a thermal death point of 55° C., are not particularly resistant to heat. The Bureau of Animal Industry recognizes 137° F. (58.3° C.) as the minimum temperature to which pork—including the interior of the piece of meat—should be cooked. Cameron [14] warns that "all pork should be cooked until the natural colour is gone." One might hesitate to eat pork at all after reading Dickman's recent findings [15] to the effect that 10 per cent of all pork sausage obtained at random in the markets of a large city contained trichinae. But Hall and Collins [9] have pointed out the value of pork from the economic and dietary angles, and have suggested methods of preparing pork products for safe consumption. A fact not generally known is that the federal meat inspection regulations no longer

require a microscopic examination for trichinae. As Pepper [16] has pointed out: "Inspection of pork [for trichinae] has proved too difficult and expensive to be carried out routinely with success. Also many families grow and butcher their own animals. Microscopic examination is necessary for satisfactory inspection and this has proved impracticable." The Bureau of Animal Industry has issued the following warning: "Dry-salt pork, pickled pork, and smoked pork previously salted or pickled, provided the curing is thorough, are practically safe so far as trichinosis is concerned, but as the thoroughness of the curing is not always certain, such meat should also be cooked before it is eaten."

If trichina infestation of pigs could be diminished, the incidence of human infestation would be correspondingly lessened. The rat has been considered responsible for much porcine trichiniasis; but most recent writers[5, 14] feel that this is not the crux of the problem. As Wright [5] has recently stated: "It is my opinion that the rôle of the rat as a source of swine trichinosis has been largely over-emphasized. The hog fed on uncooked garbage is today the major source of human trichinosis." Most authorities now agree that thorough cooking of all garbage fed to swine would materially reduce the incidence of human trichiniasis.

There have been many epidemics in which large numbers of individuals have been infected from the same meat supply. In the latter part of the

As an illustration of the widespread occurrence of mild or unrecognized cases of trichiniasis in the members of the family of patients with this disease, the charts of two families whom we studied with blood smears are shown here.



last century there were two large outbreaks in Germany, one involving 337 persons and the other 250. Two outbreaks of interest, because of the source of infection, were those described by Walker [11] in this country, due to bear meat, and by Weitz [12] in Germany, due to polar bear meat. Barrett and Sears [17] in 1938 recorded an epidemic of 73 cases with 6 deaths in Capac, Michigan with a population of only 800. Drake, Hawkes, and Warren [18] give a very good account of the history of epidemics of this disease. Spink and Augustine,[19] who have done a great deal of excellent work in Boston on trichiniasis, review the general epidemiological knowledge in a most satisfactory manner.

The mortality in various outbreaks has varied from 1 to 30 per cent, averaging about 10 per cent. The figure tends to be higher in the larger outbreaks. In sporadic cases, which are common in this country, the mortality is definitely under 5 per cent. The percentage depends to a great extent on the number of relatively symptom-free infected individuals who are included in the series. Trichiniasis would not seem nearly so scarce if we would be more thorough in investigating the families of persons found to have the disease. The inclusion of those with either very mild symptoms or no symptoms at all, in whom the diagnosis is made by a consideration of the history, physical examination, and laboratory findings, would materially lower the apparent mortality. It must be remembered that "not all persons who eat trichinous flesh have the clinical disease. A limited number of the worms may not cause noticeable symptoms." [20]

Clinical and Pathological

Immediately after the ingestion of trichinous meat there may occasionally be symptoms of a mild gastrointestinal upset, with nausea, vomiting, and abdominal pain. Twenty-four to seventy-two hours later the period of invasion begins. Anorexia, nausea and vomiting, diarrhea, and generalized abdominal pain are often present. These symptoms may be severe enough at times to resemble cholera. The incubation period—from the ingestion of the trichinae to the first symptoms—is usually given [17, 18, 21] as 2 to 27 days, with an average of about 7 to 12 days, for cases occurring during an outbreak. In sporadic cases, however, it seems to be much shorter, having been 48 to 72 hours in many of our cases. The period of dissemination begins about 6 to 10 days after eating the meat. As stated previously, the dissemination of the larvae consists of their migration from the intestinal mucosa through the lymph and blood streams.

The larvae were first found in the blood in 1909 by Herrick and Janeway [22] by diluting a sample of blood with 10 parts of 3 per cent acetic acid, centrifuging, and examining the sediment. This method is still in use, and the larvae have been found in the blood from the sixth to the twenty-second day of symptoms in almost 50 per cent of the cases in which they have been searched for. Van Cott and Lintz [23] were the first to discover the larvae

in the spinal fluid in 1914, since which time many others have found them there.[24, 25, 26, etc.] The adult worms have occasionally been found in the stools, even many weeks after the infection,[27] although this is a relatively rare finding. The larvae have also been found in the pleural and peritoneal exudates, milk of a nursing woman, and pus from a furuncle.[24] They have not been observed in the urine or in the pericardial fluid, to the best of my knowledge. Many tissues and organs may contain the embryos: the brain and meninges [28, 29, 30]; intestinal mucosa; mesenteric lymph nodes, liver, lungs, pancreas, myocardium [30]; placenta, mammary gland, kidney, retina, and bile.[28] Frothingham,[30] who gave an excellent description of the pathology of trichiniasis in 1906, based mostly on the work of Cohnheim, observed that the embryos enter the organs by "breaking out of the [blood] vessels." The site of predilection and the final resting place of most of the larvae is the skeletal musculature, where they "grow for about two weeks, when they begin to coil up and encyst. The cyst wall is distinct by the end of the sixth week and becomes complete in about three months. The capsule begins to calcify in about six months. It is believed that these embryos may live 20 to 30 years in the cyst in the human."[13] Frothingham thought that the capsule is formed of connective tissue, but MacCallum [31] considers that it is formed by the worm, as "the host does not produce such a peculiar capsule for any other foreign body."

General Symptomatology

Fever is almost always present during the acute stage of the disease. In most cases the temperature varies from 100° to 103° and lasts from a few days to several weeks. In other cases there is high fever, 104° to 106°, which may last many days. This type of fever curve, with the relative bradycardia usually present, produces a chart similar to that seen in typhoid. Chills were present in 8 of 35 cases in the series of Spink and Augustine.[32] Hypotension (systolic under 100) was noted in 12 of their cases. Sweating and itching are fairly common, according to Salzer,[33] although this is not the usual experience. Some symptoms such as fever, sweating, chills, itching, hypotension and weakness, are probably mainly due to toxemia from the presence of the larvae and from muscle destruction. Other symptoms and signs, such as dehydration, acidotic breathing, tetany, and weight loss, are attributable mostly to vomiting and diarrhea, with the consequent upset in the water and salt metabolism. Aside from the results of the toxemia and of the derangement of salt and water metabolism, the clinical picture will depend on the tissues and organs invaded by the larvae.

Gastrointestinal Tract

The presence of the trichinae—adults and embryos—in the intestinal lumen and mucosa is responsible for the gastrointestinal symptoms which are usually present during the period of invasion; i.e., second to eighth days

after eating the infected meat. About 70 per cent of patients have gastrointestinal symptoms of some sort. These consist of anorexia, nausea and vomiting, generalized abdominal discomfort or cramps, occasionally constipation but more often diarrhea, very rarely intestinal hemorrhage. The diarrhea may be so severe that, in conjunction with the fever, prostration and toxemia, cholera or dysentery may be simulated. The diarrhea and vomiting may cause marked dehydration, acidosis, weight loss, exhaustion, and even death.

Musculature

The migration of the larvae through the blood stream into the muscles results in a myositis. Clinically the muscles most often affected are the gastrocnemii, deltoids, biceps, and those around the eye; less often the diaphragm, various muscles of the extremities and of the abdominal wall and thorax; rarely but of greater seriousness, the intercostals, the muscles of mastication, deglutition, and speech; and occasionally the cardiac musculature. At autopsy the diaphragm is probably the most frequently involved; and large numbers of larvae are sometimes found in the muscles of the glottis, larynx, and tongue,[34] in addition to the muscles listed above. Invasion of the muscles of the trunk or extremities is manifested by edema, pain and tenderness. The pain, if located in the abdominal wall or back, may be severe enough to simulate a colic: renal, biliary, intestinal, etc. The tenderness may be slight or extremely marked. There may be weakness of the muscle or even paralysis, suggestive of poliomyelitis. In Spink and Augustine's series,[32] 26 of 35 patients complained of muscle pains. The eye muscles are frequently involved, causing pain and burning in the eyes, conjunctivitis, occasionally subconjunctival hemorrhages, photophobia, paresis, diplopia, and edema. Edema of the eyelids is one of the most constantly observed clinical features of trichiniasis. A history of puffy eyelids or actual edema noted on physical examination was present in almost 60 per cent of 12 ambulatory cases and in 80 per cent of 15 hospitalized patients whom I have seen in the past five years. From the viewpoint of the ophthalmologist, who is occasionally the first to see the patient, the "most characteristic ocular sign is chemosis of the bulbar conjunctiva, bilateral as a rule."[35]

Involvement of the muscles of the respiratory tract is usually serious, as life may be threatened by asphyxia due to edema of the pharynx and larynx.[36] Inflammation of the diaphragm and intercostal muscles may lead to painful breathing or respiratory embarrassment; and paralysis of the respiratory muscles may occur.[12] The muscles of mastication are sometimes the seat of edema, occasionally simulating mumps.

Respiratory System

Respiratory signs and symptoms are frequent, having been present in 50 per cent of 102 cases reported by Minot and Rackemann.[37] The pharynx, larynx, trachea, bronchi, lungs and pleura may be affected. Cough, sputum

(usually mucopurulent), dyspnea, cyanosis, signs of pulmonary congestion or consolidation, alone or together, may be present. Bronchopneumonia or lobar pneumonia may be simulated or actually present.[37] Pleurisy and pleural effusion also occur. Hemoptysis occurring during the course of an attack of trichiniasis has been reported [38] in three cases.

Nervous System

Symptoms and signs of central nervous system and peripheral nerve involvement are fairly common and may be very severe. Diplopia and paresis or paralysis of the eye muscles are not rare; and it is frequently not realized at first that the lesion is a myositis rather than damage to a cranial nerve or meningeal irritation. Reflex changes are common, the most usual abnormality being a diminution or loss of the knee jerks. These were absent in 10 per cent of the cases seen by Merritt and Rosenbaum.[39] The ankle jerks may also be lost, as well as the biceps reflex and others. Signs of meningeal irritation may be present, such as stiff neck, positive Kernig and Brudzinski signs, headache, blurred vision and diplopia.[40] Meyer [25] reported three cases simulating meningitis with trichina larvae in the spinal fluid. Blumer [26] and Merritt and Rosenbaum [39] have seen cases with hemiplegia and the larvae in the spinal fluid. Willett and Pfau [41] saw one case with a temporary paralysis of a leg; and Barrett and Sears [17] reported two cases with paralysis of the extremities. One of our cases (number 2) showed an absence of knee jerks and biceps reflexes, stiff neck and positive Kernig and Brudzinski signs, carpopedal spasm, paresis of the left side of the face, unequal pupils, and a terminal hyperpyrexia up to 109°. General signs of cerebral involvement, such as coma, severe mental depression and disorientation, may be found.[12] Peripheral neuritis occurs occasionally, although more often there is muscle weakness and pain, which may simulate neuritis or a lesion of the anterior horn cells—poliomyelitis, for example. Involvement of the cranial nerves occurs very rarely. Encephalitis due to the presence of the embryos in the brain has frequently been reported,[28, 29, 30, 42] with a variable and bizarre neurological picture, as a rule. Hassin and Diamond [29] point out that trichiniasis may produce a typical picture of acute non-suppurative meningo-encephalitis with degenerative changes due to toxins and with inflammatory changes due to the presence of the larvae. From what has been said it will be apparent that Merritt and Rosenbaum [39] summarized the situation well when they warned that cases of trichiniasis with neurological manifestations must be differentiated from poliomyelitis, encephalitis, encephalomyelitis, meningitis, polyneuritis, dermatomyositis, and periarteritis nodosa.

Cardiovascular System

Cardiovascular complications have been stressed clinically only during the past few years, mainly by Spink and Augustine.[32, 43] Symptomatically

there may be dyspnea and orthopnea, cyanosis, palpitation and tachycardia. On examination one may find the signs of congestive heart failure or merely of a myocardial involvement, such as a systolic murmur at the apex, poor quality of the sounds, tachycardia, hypotension, irregularity of rhythm. An acute myocarditis, which has been demonstrated pathologically in humans and in animals, accounts for these signs and symptoms. The myocarditis is caused by the presence of the larvae in the myocardium, producing an inflammatory reaction.[43, 44] Hypotension (systolic under 100) was present in 12 of Spink and Augustine's 35 cases. Other vascular changes include congestion and hemorrhages in the conjunctivae and sclerae, lungs, and gastrointestinal tract. Edema in various parts of the body is probably largely a manifestation of capillary damage. Thrombosis, phlebitis, and embolism, including pulmonary, have been noted.[12, 43] Electrocardiographic changes were found in 6 of 17 patients in whom tracings were taken by Spink and Augustine.[32] The changes consist of: inversion of the T-wave, especially in Lead II; low amplitude of the QRS complex; and occasionally evidence of intraventricular block. Beecher and Amidon [45] saw one case with temporary nodal premature contractions, and another with temporary prolongation of the P–R interval. Death from myocarditis usually occurs from four to eight weeks after the onset of the illness.[43] An interesting observation is the relatively frequent occurrence of encephalitis and myocarditis in the same patient [29, 30, 42] (see also case 12 in this paper).

Skin

Skin manifestations are noted frequently in some series and rarely in others. Weitz [12] says that most of his 88 cases (from polar bear meat) had a rash; and Spink and Augustine [32] record a skin eruption in 5 of 35 cases. On the other hand, in 35 sporadic cases—ambulatory and hospitalized—which we have recently seen at the Lenox Hill Hospital, there is no record of a rash or eruption in a single one. Among the 35 Boston cases two patients had a scarlatiniform rash, two had a rash "resembling rose spots," and one had an erythema multiforme. In Weitz' series most of the patients had an exanthem resembling that of measles or scarlet fever, usually beginning during the third week of the illness. A scarlatiniform enanthem with a "strawberry tongue" sometimes occurred as well.

McNaught [46] has recently reported the occurrence of subungual "splinter" hemorrhages. The observation of this phenomenon was made by Briggs, who noted it in "at least 12 of the last 20 cases" seen by him.[47] "The hemorrhages are the same as those occasionally seen in subacute bacterial endocarditis, only much more numerous. They are absolutely without pain."[47] These splinter hemorrhages probably represent emboli composed of trichina larvae.

Genito-Urinary Tract

The kidneys occasionally show involvement, as manifested by finding albumin and casts in the urine. These findings are probably merely the result of toxic changes, although larvae have been found in the kidneys at autopsy. I have found no reference to the occurrence of a true acute hemorrhagic nephritis in this disease. At autopsy there may be "congestion, edema, cloudy swelling, and tubular degeneration."[10] The larvae have not been found in the urine, nor in the musculature of the ureters or bladder. Inflammation of the ureters and bladder does not occur, and the genital organs also escape infection, so far as I am aware.

Parenchymatous Organs

The liver shows fatty changes at autopsy,[34] and the larvae have been found therein.[30] There are no references to hepatitis or jaundice during the course of trichiniasis. The spleen is frequently enlarged, but no distinctive postmortem changes are reported, other than "parenchymatous degeneration."[10] Larvae have been seen in the pancreas at autopsy,[30] but pancreatitis has not been described as occurring clinically. Although the embryos have been found in the bile, cholecystitis does not occur.

Organs of Special Sense

In the eye muscles the larvae are often embedded, causing various eye abnormalities, as mentioned previously. The larvae have been found in the retina.[48] Permanent damage to vision has never been reported, to my knowledge. Otitis media has occurred as a complication of trichiniasis.[12] The semicircular canals may apparently be involved, either by toxins or by the presence of larvae, as vertigo and tinnitus occur on occasion. I have read of no cases of deafness resulting from this disease. Although the muscles of the tongue are sometimes affected, the sensation of taste does not seem to become impaired.

Bone Marrow

A mild infection with trichinae stimulates the production of eosinophilic myelocytes and mature eosinophiles in the bone marrow; but a severe infection, especially a fatal one, causes a destruction of the eosinophilic cells, as was found many years ago by Opie.[49]

Lymph Nodes

The mesenteric lymph nodes show enlargement, an accumulation of eosinophiles, and occasionally the presence of the larvae, especially in the early stages of the disease.[30, 31] The tracheo-bronchial nodes are similarly affected, although to a lesser degree. Most of the other lymph nodes do not show these changes.

Miscellaneous

Larvae have been found in excised mammary gland tissue, human milk, and placenta.[24, 28] No distinctive pathological changes have been reported in the thyroid, parathyroids, pituitary, or adrenal glands. Nor in the joints, synovial membrane or fluid, fatty tissue, salivary glands, hair, teeth, or bones, other than in the marrow.

Physical Examination

The findings on physical examination in trichiniasis are extremely variable, as would be expected from the description of the symptomatology and pathological findings. Evidence of fever, such as warm, moist and flushed skin, and tachycardia are often present. Edema of the eyelids is one of the most constant signs. Conjunctivitis, congested sclerae, subconjunctival hemorrhages are frequently noted. Paresis of the eye muscles is more rare, but may be very misleading, especially if associated with stiff neck and painful neck muscles. Papilledema is noted in some patients who have cerebral edema. Tenderness and occasionally edema of skeletal muscles, especially the gastrocnemii, biceps and triceps, are very common findings. Congestion of the pharynx is noted rather frequently. Abdominal tenderness, sometimes marked, may be localized to any portion of the abdominal wall, and may be the source of considerable confusion in diagnosis. Enlargement of the spleen was recorded on admission in 9 of 21 cases in our hospital. In a series of 10 cases reported by Reifenstein, Allen and Allen,[50] four patients had a palpable spleen during the third week of the illness, while in seven the spleen could be felt five months after the onset of the illness. Reflex changes of all sorts, especially a positive Kernig sign and absent knee jerks, are common. Somnolence, delirium, coma, mental depression and disorientation are occasionally seen. Evidence of neuritis occurs rarely. Dyspnea, cyanosis, paralysis of the respiratory muscles are noted in unusual cases. Cough and expectoration, as well as signs of bronchitis, bronchopneumonia or lobar consolidation, pleurisy or pleural effusion, may be present. Rashes simulating the rose spots of typhoid or the eruption of measles, scarlet fever, German measles, or erythema multiforme have been recorded.[12, 32] A scarlatiniform enanthem and a "strawberry tongue" have been seen.[12] There may be hypotension, and the heart sounds may be of poor quality. In severe cases, in which there has been much diarrhea, one may detect evidence of dehydration, acidosis, and weight loss. There is frequently high fever and the patient may present the appearance of marked prostration and toxemia. Hemiplegia or loss of power of an arm or leg have been reported [17, 26, 39, 41] (case 12). Tetany (case 2) and choreiform movements have been noted.

Laboratory Examinations

There are numerous laboratory procedures which will suggest, help to confirm, or definitely prove the diagnosis of trichiniasis; and in this disease

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the laboratory is of particular aid in supplementing the history and physical examination. The trichina larvae have frequently been found in the blood and spinal fluid; rarely in the stool; and as a curiosity in the bile, milk of a nursing woman, pleural exudate, and pus from a furuncle. In the blood the larvae are discovered by diluting 5 to 10 c.c. of venous blood with 10 times its volume of 2 per cent acetic acid, centrifuging, and examining the sediment. The larvae are easily recognized, being 125 μ long and 6 μ broad, and not likely to be confused with any other structures. One may find them in the spinal fluid by merely centrifuging the fluid. Evers [51] points out that larvae are present in the spinal fluid in many cases, regardless of the presence of neurological signs. The spinal fluid, when larvae are present, will usually show increased pressure and increased cells—mostly lymphocytes up to 40 to 240 per cubic millimeter. Even when embryos are not present, there may be an increase in the pressure and in the number of cells. The larvae are best found in the stools by making them alkaline and waiting 12 to 24 hours before examining the liquefied stool.[24] According to Salzer [33] the feces are usually clay-colored, as a result, he surmises, of a reduction of bilirubin by the living trichinae. Others have not noticed or mentioned clay-colored stools.

Blood Cells

The blood examination in trichiniasis is extremely important and interesting. The red blood cells and hemoglobin are not usually affected during the illness; and the main changes are in the white blood cells. There is usually a leukocytosis, sometimes to a very high figure. One of our cases had 36,000 white blood cells, which seems high until one reads of a case of van Cott and Lintz's [23] which had 75,000. The average figure is about 12,000 to 18,000. On the other hand there may be a leukopenia, relative or absolute, especially frequent in children. One of our cases, for example, had a total leukocyte count of 4,000 with a temperature of 101°, and another had 6,000 with a temperature of 105°. There is usually an absolute and practically always at least a relative increase in the granular cells (which include the eosinophiles). An outstanding characteristic of the smear is a moderate to marked increase in the percentage of immature polymorphonuclear leukocytes—the so-called "shift to the left," which may be quite noticeable, even up to 50 per cent, although the average is about 25 to 35 per cent.

The most important, constant, interesting, and diagnostic laboratory finding is the eosinophilia. It may reach astounding figures, such as 83 per cent in a case of van Cott and Lintz's, and 81 per cent in a case I saw several years ago in the New Haven Hospital. Drake, Hawkes, and Warren [18] report one patient with a total of 34,000 white blood cells and 70 per cent eosinophiles, and van Cott and Lintz speak of one with 75,000 white blood cells and over 60 per cent eosinophiles. There are a few other con-

ditions in which such extreme figures may be seen: other parasitic infestations, such as *Tenia echinococcus;* some allergic conditions, such as angioneurotic edema; eosinophilic leukemia; periarteritis nodosa; and familial eosinophilia. But it is most unlikely that any of these diseases would cause confusion in the diagnosis of a case of trichiniasis; and it is well to remember that trichiniasis is the only disease which shows an eosinophilia during the acute febrile stage, with the exception of allergic asthma and infectious mononucleosis, and the extremely rare cases of eosinophilic leukemia and periarteritis nodosa. Of course lesser degrees of eosinophilia—5 to 25 per cent—are frequently seen in diseases other than those already mentioned. Among these are: all other intestinal helminth infestations; allergic diseases, such as pollenosis, urticaria, serum sickness, and above all asthma; skin diseases, such as pemphigus, psoriasis, secondary syphilis, and eczema, especially of the allergic type; the convalescent stage of some acute infections, such as scarlet fever and rheumatic fever; Hodgkin's disease, in which the eosinophilia may occasionally rise to very high values; and some miscellaneous conditions, such as nirvanol sickness, polycythemia vera, after certain drugs in sensitive persons, and after foreign protein injections at times.

What is the mechanism of the eosinophilia in all these varied conditions? It seems to be essentially a stimulation of the eosinophilic myelocytes of the bone marrow by certain proteins or protein breakdown products formed in the tissues. As Whitby and Britton [52] say: "The stimulation of eosinophils by protein affords a reasonable although a not yet complete explanation of most of the processes which have been found to cause the phenomenon of eosinophilia. . . . It seems probable that post-febrile eosinophilia is the result of stimulation of the bone marrow by the protein products set free during the process of inflammation. So long as the inflammatory process is in existence eosinophil production is depressed, but once the acute toxic stage is over, then the marrow is able to react to the stimulus of the protein products resulting from the inflammatory process." Opie [49] showed many years ago in guinea-pig experiments that the administration of trichinae stimulates an active multiplication of the eosinophilic myelocytes and mature eosinophiles of the bone marrow with subsequent blood and tissue eosinophilia. This occurs at a time when the larvae are being transmitted from the intestinal mucosa through the blood stream into the muscles and other tissues. A breakdown protein product is probably formed by the interaction of the larvae and the muscle proteins, which acts as the stimulus to the multiplication of the bone marrow eosinophilic elements.

The first reference in the literature to the eosinophilia of trichiniasis is that of Brown [53] in 1898, who found a marked increase in the percentage of these cells in the blood of three patients on the wards of the Johns Hopkins Hospital. The discovery probably came at this time because differential blood smears were becoming increasingly more common since the intensive work of Ehrlich on blood cell morphology and staining in the years following 1879.

What constitutes blood eosinophilia in humans? Drake, Hawkes, and Warren set the upper limit of normal at 500 per cubic millimeter (10,000 white blood cells with 5 per cent eosinophiles). Spink and Augustine set 400 as the limit. I cannot agree with either group that there is a definite figure, as it seems to me that the percentage is considerably more important diagnostically than the total. Thus a leukocyte count of 18,000 with 3 per cent eosinophiles, giving an absolute figure of 540 per cubic millimeter, I would not call a definite eosinophilia; conversely a total leukocyte count of 4,000 with 6 per cent eosinophiles, giving an absolute figure of only 240 per cubic millimeter, I would call a definite eosinophilia. An eosinophile count of 4 per cent I consider suspiciously high and as the upper border of normal, and 5 per cent abnormally high, irrespective of the total leukocyte count.

In animal experiments the eosinophilia of trichiniasis does not appear until the muscles are invaded.[49] This seems to be the case clinically as well, since the eosinophilia usually begins during the second week of the illness, which is the period when the larvae are being disseminated through the body. Aldridge[54] mentions two cases in which the eosinophilia developed on what seemed to be the fourth and ninth days after the ingestion of trichinous meat. Sometimes the increase may not be noted until the third week or later.[32, 55] Some cases have a low eosinophile count, a sudden drop, or no eosinophiles whatever throughout the illness, although these are very rare occurrences. In fatal cases there is usually a complete absence of eosinophiles, especially if the course of the disease is rapid. Aldridge described two such cases, Spink and Augustine one, Sobel one, and others have been reported. Opie found experimentally that in severe and fatal infections with trichinae there is a degeneration and destruction of the bone marrow eosinophilic elements. Complicating secondary infections will cause either a delay in the appearance of the eosinophilia or a drop in the percentage, if it was previously elevated. Drake, Hawkes, and Warren report a count of 34,000 leukocytes with 70 per cent eosinophiles in a child when he was afebrile and apparently convalescing. Two days later he developed a cough and fever, and the count then was 31,600 white blood cells with 8 per cent eosinophiles—a decrease in these cells from 23,800 to 2,500 per cubic millimeter. They mention another case, a male of 40 years, who had 12,000 white blood cells with 24 per cent eosinophiles, who, shortly after—on the day of death—had 16,800 white blood cells with but 1 per cent eosinophiles. On the other hand the same authors note the unusual occurrence of a count of 23,100 white blood cells with 38 per cent eosinophiles in a woman of 45 on the day of her death from pneumonia. Spink[56] found that in trichinized animals secondarily infected with bacteria the number of circulating eosinophiles is decreased, but that heat per se does not cause a reduction. A lack of eosinophilia may be noted not only in severe and fatal cases, but also under the following conditions: in patients with secondary infections; at a very early stage in the disease; possibly in an occasional individual whose bone marrow does not

respond in the usual manner, such as one who is suffering from lymphatic leukemia; and finally when there are technical errors in the blood smears. This last may sound like an academic point, but sometimes it is of practical importance and the cause of confusion in diagnosis, as I have observed on several occasions. Freshly made solutions of Wright's stain are usually too alkaline and bring out the eosinophilic granules poorly; and these weakly stained granules may lead the inexperienced to classify these cells as neutrophiles. It is well to remember that eosinophilic granules are best brought out by a short period of staining; i.e., leaving the water on the slide for only about 45 seconds. If the Wright's or other polychrome stain has been poorly made, it may give totally misleading results so far as eosinophilia is concerned.

Fluctuation in the eosinophilia in trichiniasis may at times be marked, changing from a high percentage to a low one or vice versa in a few days. There seems to be no definite relation between the severity of the illness and the height of the eosinophilia, except that, as mentioned before, the very severe and fatal cases usually show a low percentage or no eosinophiles at all. Some mild or asymptomatic cases have a count of 40 to 50 per cent; a case of moderate severity may have 15 per cent or 60 per cent; a severe case may have 70 per cent or none. As an example of the fluctuations that may occur in a short time, one of our cases had an eosinophilia of 31 per cent on admission after two days of symptoms; four days later this rose to 63 per cent; in another seven days this had fallen to 40 per cent; and finally after another seven days to 12 per cent. Weitz [12] says that there are two peaks to the eosinophile curve: one at the beginning of the illness and another at about the time the patient has convalesced enough to leave the hospital. Although this occurs in some patients, it is by no means the rule. There is considerable difference of opinion concerning the question of how long the eosinophilia lasts. I have collected a group of cases from various articles [17, 35, 42, 50, 57, 58, 59] (and my own series) in which differential counts were done at various times after the onset of the illness. In 44 cases the highest eosinophilia early in the disease averaged 34 per cent. In 21 of these cases in which counts were performed three months later, the average had fallen to 12 per cent, with none as high as the initial maximum. There were 10 patients who had smears made about 4½ months after the beginning of the infection, and these counts were on the average about one-sixth of the initial average high: 6 per cent. Thirteen counts were repeated six months from the onset and averaged 5 per cent, with only one above 9 per cent. At 8 to 12 months 12 cases all showed 5 per cent or less and averaged 2.5 per cent, which is within normal limits. In summary it may be said that most cases will show only a slight eosinophilia—5 to 6 per cent—six months after infestation, and that practically all will have normal figures after 8 to 12 months.

Sedimentation Rate, Blood Chemistry, Widal Test

Determinations of the erythrocyte sedimentation rate in trichiniasis have not been recorded in the literature. Unfortunately, this determination was made in only four of our cases. The results in two were well within normal limits, in one the rate was slightly increased, and in one it was moderately increased. All of these patients had fever and were acutely ill with uncomplicated cases at the time the sedimentation rate was determined. While four cases is too small a number from which to draw conclusions, it would seem that a marked increase is not the usual finding, even during the acute febrile stage.

The blood chemistry values are within normal limits in most uncomplicated cases.[60] Some observers have claimed that there is a decrease in sugar tolerance, but a review of the work is not at all convincing; and all our patients who had fasting blood sugar determinations showed normal values. The one type of blood chemistry abnormality which one may expect to encounter is that associated with vomiting, diarrhea, and dehydration; i.e., lowered CO_2 combining power, slight increase in the non-protein nitrogen, and occasionally evidence of loss of fixed base, such as a low serum calcium or sodium.

The Widal test may occasionally be positive, even in high dilutions.[55] This may sometimes be a source of confusion, as will be pointed out later.

Intradermal and Precipitin Tests

In 1928 Bachman[61] described an intradermal test for trichiniasis. Trichina larvae obtained by digestion of infected meat are desiccated, and the powder is prepared in dilutions of 1:500 and 1:10,000 with Coca's solution. 0.01–0.05 c.c. is injected intradermally and the reaction is read in 15 to 30 minutes. A positive reaction is similar to that produced by other allergens with intracutaneous testing; i.e., a wheal with or without pseudopodia, a surrounding zone of erythema, warmth, and sometimes itching. The test is much more specific when done with a 1:10,000 dilution, and this is the strength which should be used in order to get a minimum of false positives. The investigators[21, 58, 62, 63, 64] who have had the most experience with the test feel that it is a definite aid in diagnosis, especially when a negative reaction early in the disease turns positive during the course of the illness. There is a theoretical possibility that repeated tests with the antigen might provoke a falsely positive result in a person not suffering from trichiniasis. Repeated intradermal injections of the antigen into a small group of doctors showed the author that negative tests do not thereby become falsely positive.

A negative test is more useful in ruling out trichiniasis than is a positive one in establishing the diagnosis. A positive test may result from trichinous infestation many years before,[58] from other parasitic infestations,[62] or may

be found, although rarely, in persons who give false-positive reactions to all intradermal tests. Schapiro, Crosby, and Sickler [64] found a close correlation between the skin test findings and the postmortem findings in a large series of cases. One drawback of the intradermal test is the fact that it does not become positive, as a rule, until between the fourteenth and twentieth days of illness; sometimes not until even later; and occasionally not at all. Until recently it was difficult to obtain the antigen, but now one can get vials of the 1 : 10,000 dilution from the National Institute of Health.

The precipitin test is at least as accurate as the skin test,[32] develops slightly later—about the fourth week—and may also remain positive for many years.[58] In a recent series of 44 hospitalized cases of trichiniasis, 100 per cent gave positive intradermal and precipitin tests.[21] Serum may be sent to the laboratory of the National Institute of Health for the precipitin test.

Biopsy

The biopsy is an inconvenience to the patient, but it is not a dangerous procedure and usually does not prolong the hospital stay very much. Evers [51] suggests examination of a centrifuged specimen of spinal fluid whenever biopsy is contemplated, since finding the larvae in the fluid will obviate the necessity of an operation. Biopsy is of some importance in the final diagnosis, although even when it is negative, one may be entirely justified in making the diagnosis of trichiniasis on clinical grounds. But a positive report will definitely confirm the diagnosis. Hall [6] pointed out that the tissue excised should be examined as a press preparation rather than as sections, since the former is more certain and rapid. More recently Queen [65] recommended the digestion in artificial gastric juice of biopsy and necropsy material and suspected meat products.

In our series there were 15 positive biopsies out of 17 performed, a fairly high percentage. It must be said, in all fairness, that almost all of the 15 positive cases had been rather definitely diagnosed as trichiniasis before the operation, and that the two patients with negative biopsies are still considered by us as definite cases. So I cannot agree with those who say that the biopsy is of extreme importance, but am more of the opinion of Spink and Augustine,[32] who believe that "the biopsy is an unnecessary procedure, not only because of the uncertainty of finding the parasites in a small piece of muscle, but also because the precipitin and skin tests are as reliable as the procedure of biopsy, which is, of course, an inconvenience to the patient." However, the skin and precipitin tests are not by any means infallible, and may be positive from a trichinous infection long before the present illness. Finally, while Spink and Augustine and also Sobel say that the larvae may be missed in a biopsy, actually the biopsy was reported as positive in 12 of 13 cases in Spink and Augustine's series and in 6 of 7 in Sobel's, for a total of 90 per cent correct positives, which is a very good record for any laboratory procedure in medicine.

Diagnosis

The diagnosis of trichiniasis is frequently a difficult matter, and the percentage of correct diagnoses on first seeing the patient is not high. In the 35 cases in the Boston series,[32] the preliminary diagnosis after the history and the physical examination, but before any laboratory data were obtained, was right in only 11 cases or 31 per cent. In our series, trichiniasis was definitely diagnosed on admission, before obtaining the blood count, in 7 of 21 patients or 33 per cent, although the disease was mentioned in the admission note as a possibility in 5 others or in an additional 24 per cent. Hall [6] has pointed out that "the classical picture as given in the textbooks is greatly oversimplified and represents only a composite picture." The typical case is not often seen; and trichiniasis is characterized by the lack of regularity of its manifestations and course. As in many other obscure diseases, merely thinking of the possibility will help considerably in arriving at the diagnosis. Then one must take a careful history, with specific questioning relative to any recent ingestion of pork products. Inquiry must be made concerning any recent illness suggestive of trichiniasis in other members of the family.

Suspicious symptoms are: edema of the eyelids, which should cause one to consider a diagnosis of trichiniasis until the edema is proved to be due to some other cause; muscular pains, fever, nausea, vomiting, generalized abdominal pain, diarrhea or constipation, chills and sweats, headaches, diplopia, pain and redness and burning in the eyes, dyspnea and other pulmonary symptoms. Important points in the physical examination are: edematous eyelids, muscular tenderness and swelling, fever and tachycardia, conjunctivitis and subconjunctival hemorrhages, paresis of the eye muscles, abdominal tenderness, enlarged spleen, signs of meningeal irritation and of encephalitis, evidence of dehydration, hypotension, and signs of pulmonary congestion or consolidation.

The most suggestive laboratory finding, and in fact, the thing which most often calls one's attention to the correct diagnosis, is the eosinophilia. A very important confirmatory finding is an eosinophilia in other members of the family, especially if it is accompanied by suggestive signs and symptoms, and if there is no allergic history to explain the eosinophilia. The total leukocyte count and the shift to the left are not very helpful diagnostically, except when considered in conjunction with the eosinophilia. The intradermal and precipitin tests are of considerable aid, but become positive only many days after one would like to make a diagnosis. Final proof of the diagnosis depends on finding the larvae in the blood, spinal fluid, or in a piece of muscle at biopsy. Spink and Augustine feel that "the most reliable diagnostic aid is the eosinophilia." With this I agree, if one is speaking of the presumptive clinical diagnosis. Final proof cannot depend only on an eosinophilia, of course. Blumer [26] says: "Any febrile disease which is accompanied by edema of the eyelids and evidence of involvement of the muscles

at once calls for a blood count." I would go further and suggest that any obscure illness warrants a differential blood smear, repeated several times, if necessary. Finally it should be borne in mind that a negative biopsy, the failure to find the trichina larvae in the blood, spinal fluid, or stools, a negative skin or precipitin test, or the absence of eosinophilia does not rule out the diagnosis of trichiniasis.

Differential Diagnosis

One of the most interesting and amusing aspects of the study of trichiniasis is the astounding variety of diseases with which it has been confused. Rather than merely listing the conditions which have been diagnosed by mistake, it will be more instructive to group them according to the symptoms or signs which caused the error. The gastrointestinal manifestations, with nausea, vomiting, diarrhea, and abdominal pain, which are so common early in the disease, may simulate: infectious gastro-enteritis, ptomaine or food poisoning, " intestinal influenza," colitis of various types, dysentery, and even cholera.[6, 32] The fever, especially when associated with muscle pains as it usually is, may cause one to diagnose grippe or influenza. When the fever is very high and the course of the illness fulminating, septicemia may be suspected, as in one of our cases (number 2). When the fever is prolonged, undulant fever and pulmonary tuberculosis have been considered.[32] A common error, especially in former years, was to call the illness typhoid fever, which is quite understandable in view of the occurrence at times of high sustained fever with no localizing signs, bradycardia, enlarged spleen, positive Widal test, and even an eruption resembling rose-spots—although all these in the same patient would be distinctly unusual[37, 41, 55] (case 5 in this paper). Sometimes the hospital chart is signed out as " Fever of Unknown Origin "[66] (case 10).

The edema of the eyelids has often resulted in an initial diagnosis of acute nephritis or acute sinusitis, and more rarely of angioneurotic edema, especially because of the associated eosinophilia[16, 32] (cases 6 and 9). The edema of the masseters has on occasion suggested a diagnosis of mumps[54, 50] (case 3). Myositis, especially when combined with fever, causes considerable confusion. Rheumatic fever and acute generalized arthritis of various kinds are often mistakenly diagnosed. Involvement of the masseter muscles has caused physicians to decide that the patient was suffering from tetanus.[16, 32] When the abdominal muscles are attacked, bizarre and often serious errors of diagnosis may ensue. Acute appendicitis[66] or an " acute surgical abdomen " may be suspected, and an unnecessary operation may be performed. A less serious error is the tentative diagnosis of gall bladder disease[6] or peptic ulcer.[55] With myositis in the back, renal colic has been simulated (case 4 and another unreported case in our series). Any other type of colic may likewise be erroneously diagnosed.

Neurological signs and symptoms occur frequently enough to cause con-

siderable confusion, and the following have been diagnosed at various times: poliomyelitis, especially when there is associated muscle pain and weakness; encephalomyelitis and encephalitis,[39] which may actually be present due to the trichina larvae; tuberculous meningitis [32] and pyogenic meningitis [39]; polyneuritis [12, 39]; polymyositis [67]; periarteritis nodosa [39]; chorea (case 11); and cerebral thrombosis resulting in hemiplegia.[26]

Cardiac involvement makes one think of rheumatic endocarditis and myocarditis [32] (case 11), or of a myocarditis of unknown etiology.[6] Pulmonary signs and symptoms have resulted in the diagnosis of lobar or lobular pneumonia or pleurisy, any of which in fact may actually be present.[37] Other miscellaneous diagnoses have been reported,[6, 32, 41, 55] such as: pelvic inflammatory disease, paratyphoid fever, malaria, erysipelas, syphilis, and others.

The *commonest* incorrect diagnoses are: grippe and influenza, acute nephritis or sinusitis, typhoid fever, and rheumatic fever. When one realizes the large number of cases which are not correctly diagnosed for many days or weeks even when under close observation in the best hospitals, one wonders how many cases must be missed in mildly ill persons in private practice. Many of these overlooked cases are, I believe, labelled with that solution to the doctor's diagnostic dilemma—grippe.

Prognosis

The prognosis in trichiniasis, as in other diseases, depends on a number of factors. First, although probably not most important, is the number of trichinae in the infected meat and the amount of meat eaten. Perhaps achlorhydria is a favorable condition for the patient; in fact, it is conceivable that the disease will not develop in such individuals, as the capsule around the larvae may not be digested with a liberation of live trichinae. Early vomiting and diarrhea are theoretically favorable events, as then fewer larvae will remain in the intestinal tract. However, it seems that this must be a minor point when one considers how very many larvae (about 1,000) develop from each adult female. Another consideration is the general health and resistance of the host, although this is naturally a difficult matter to assess. To my mind, by far the most important element in the prognosis is the fortuitous *localization* of the larvae. In the gastrointestinal tract, a severe diarrhea with its resulting dehydration and blood chemistry disturbances, may be a large contributing factor to a fatal outcome. In the musculature, a great deal depends on which muscles are affected and to what extent. A myositis with edema or paralysis of the diaphragm, intercostals, muscles of the glottis, larynx and trachea, and those of mastication and deglutition, adds greatly to the danger of the disease. Patients may die of respiratory paralysis as a result of such a localization. If the cardiac musculature is involved, the prognosis is obviously worse than if the heart is spared. Migration of the larvae into the brain is serious, and the mor-

tality in cases with encephalitis is high, as would be expected. Pulmonary involvement with pneumonia and pleural effusion naturally adds to the gravity of the condition. Why the larvae localize in different organs and tissues in various individuals is no more known than why organisms do the same thing in bacterial diseases.

Aside from the above considerations, one must take into account the degree of dehydration and acidosis; the amount of toxicity; perhaps the height of the temperature; and finally the complications. There may rarely be hemorrhages, especially cerebral, gastrointestinal, and pulmonary; abscess formation; secondary bacterial infections, etc. A fatal peritonitis complicating trichiniasis has been reported.[41] Barrett and Sears[17] saw three cases of acute appendicitis occurring during attacks of trichiniasis. The only laboratory determination of value prognostically, aside from the blood chemistry derangements that may be present, is the degree of eosinophilia. If the eosinophiles are very low or absent or falling suddenly, a serious condition is usually present; otherwise the total or percentage of these cells means nothing prognostically.

Treatment

The treatment may be divided into three aspects: specific, symptomatic, and convalescent care. Chemotherapy has been tried with very little success and has been almost entirely discarded. The most used chemical in former times was silver arsphenamine[68]; but the results were not impressive. Miller, McCoy, and Bradford[69] conducted a series of well-controlled experiments on rabbits in 1932, which dealt a severe blow to the claims of the chemotherapeutists. They found that the intravenous injection of neoarsphenamine, antimony potassium tartrate, acriflavine, rivanol, gentian violet, metaphen, and Lugol's solution had no effect whatever on the disease, and concluded that "the therapeutic rationale of the injection of such drugs in the treatment of trichiniasis is questionable." More recently McCoy[70] found sulfanilamide of no value in trichinous rats. Perhaps it is fortunate that a parasiticide has not been discovered, since one must consider the possibility of severe embolic or allergic phenomena following a rapid destruction of large numbers of trichinae, as suggested by van Someren[71] in his recent authoritative review of the treatment of trichiniasis.

The use of human convalescent serum was recommended by Salzer[24, 33] as early as 1916, and he saw what he considered some good results with it. In spite of the claims of Schwartz,[72] based only on animal experiments, that convalescent serum is of no value, Blumer[26] feels that "the quest for an effective antitoxic serum offers a more hopeful solution [than chemical agents]." With this I agree, as we have seen in recent years the remarkable value of a number of different antitoxic sera. It seems likely that the toxemia of trichiniasis would respond to human convalescent serum, but that the tissue and organ changes, such as myositis, myocarditis, encephalitis,

would not respond to anything other than symptomatic treatment. Some cases are predominantly of the toxic type and warrant a further trial of serum therapy when this is available. With this statement van Someren [71] as well as Culbertson and Kaplan [73] are in agreement.

Wantland [74] reasoned that "if cyst formation and subsequent calcification could be hastened, this would shorten the critical period in trichinosis and more quickly terminate the disease. The treatment of trichinous rabbits with irradiated ergosterol and calcium lactate has a definite therapeutic value. It remains to be tested in human cases of trichinosis." In a later article [75] the same author showed that calcification of the cysts in trichinized rats could be hastened, but admits that ergosterol in the necessary large doses is definitely toxic. Brand, Otto, and Abrams [76] recently showed that "calcification of trichina cysts parallels calcification in other host tissues." And with wise clinical judgment they conclude: "We feel then that any attempt at forced calcification as a therapeutic measure in trichinosis is not only futile with the usual human dose of parathormone, irradiated ergosterol, or related substances, but that any serious attempt to increase the doses of such substances to calcifying levels would be exceedingly dangerous."

Symptomatically one should first of all confine febrile patients strictly to bed, as emphasized by Anderson.[13] An initial cathartic should be given if the case is diagnosed very early while the larvae are still in the intestinal lumen. Usually, however, the diagnosis is not made until the larvae have burrowed into the mucosa, at which time a cathartic is of no value. Vermifuges have received little attention, but do not seem promising for the same reason. However, van Someren [71] recommends the clinical trial of Butolan, an anthelmintic, especially during the first two or three weeks of the disease. Diarrhea may be severe enough to require opium, although usually bismuth salts and kaolin suffice. Large amounts of fluid are indicated to help overcome the toxemia and replace fluids lost by vomiting and diarrhea. Sodium chloride should be given freely for the same reasons and because much salt may be lost in sweating. Calcium gluconate intravenously has been used with apparently good results by Sogemeier [77] during the acute febrile stage. Muscle pains can usually be controlled with salicylates. In the presence of myocarditis, fluids should be somewhat restricted and carbohydrates increased. The symptoms of encephalitis and meningismus may be helped by spinal taps to relieve the increased pressure. In the rare cases showing paralysis of the diaphragm and intercostal muscles, a respirator may be lifesaving.

In protracted cases the nutrition may be considerably disturbed, and the patient may become emaciated and anemic. In such cases iron preparations are indicated as well as some form of tonic. Of all acute illnesses, trichiniasis is perhaps the one in which the use of glycine as a convalescent tonic is most rational, as this amino acid has been shown [78] to enhance the capacity for muscular activity. In mild cases the patient is ill for only two to three

weeks; but in severe cases convalescence is not complete until after many months in some instances. These cases must receive a high caloric diet in addition to iron and tonics.

Summary

1. A general review of various aspects of trichiniasis is given, and the high incidence of the disease pathologically and clinically is indicated.

2. A description of the parasite and its development, the methods of human infestation, the prevention of the disease, a history of outbreaks and the mortality are discussed.

3. A clinicopathological study is presented, with special emphasis on the fact that symptoms and signs depend largely on the localization of the larvae.

4. The value of numerous laboratory examinations is assessed, and stress is placed on the diagnostic importance of a blood eosinophilia.

5. The important points in the diagnosis and differential diagnosis are emphasized, especially the occurrence of puffy eyelids and muscle pain.

6. Prognosis and treatment are considered.

7. From a series of 35 sporadic cases of trichiniasis, 12 are abstracted to illustrate various interesting points and mistakes in diagnosis.

Case Reports

Case 1. Typical severe type.

A 37 year old male. History of 17 days of severe diarrhea—20 to 25 stools daily—without blood; general abdominal discomfort; chills and fever (amount not known). Four days of very puffy eyelids with pain and burning in the eyes. Three days of pain and tenderness in the muscles of the back, chest, arms, and legs. Loss of 22 pounds in weight. Ate cooked pork about four days before onset of symptoms. On examination there were found: edematous eyelids, injected conjunctivae, palpable spleen, slight epigastric tenderness, muscular tenderness in arms and legs, and evidence of dehydration and weakness. The admission diagnosis was: Trichiniasis. The leukocyte count was 36,000 with 51 per cent polymorphonuclears (of which 17 were immature), 12 per cent lymphocytes and 37 per cent eosinophiles. The eosinophilia increased to 58 per cent on the ninth day in the hospital, decreased to 36 per cent a few days later, and to 1 per cent in eight months. The temperature ranged from 101° to 104° for three days; then from 100° to 102° for the next five days, and remained normal after that. The diarrhea was controlled within three days. Muscle biopsy was positive. The patient's wife had "grippe" at home for two weeks, and was later found to have an eosinophilia of 45 per cent.

Case 2. "Septicemia."

A 4 year old female.* The child was well up to two days before admission when she began to complain of sore throat and abdominal pain. This was followed by vomiting, which lasted several hours. She then developed fever, ranging from 102° to 106°. Swelling of the eyelids and cheeks was noted. A 12 year old sister and a 4 year old twin brother were said to have swelling of the face and eyelids at this time. On examination the patient looked seriously ill, with a temperature of 105°, a pulse of 134, and respirations of 54. The pharynx was slightly injected. The knee jerks and biceps reflexes were absent. On the dorsum of the right hand a small

*Cases 2, 3, 5 (second admission), 6 and 7 have previously been reported from this hospital by Sobel.[10]

infected, but apparently healing area was seen. The rest of the examination was negative. The admission diagnosis was: Pneumonia (?) and toxic nephritis (?). The leukocyte count on admission was 9,450 with 79 per cent polymorphonuclears (of which 47 were immature), 21 per cent lymphocytes and no eosinophiles. The urine showed a moderate amount of albumin, many hyaline and occasional granular casts, and a trace of acetone. The blood chemistry was as follows: Urea N 13.8; creatinine 0.5; uric acid 5.4; sugar 84 mg. per cent; CO_2 combining power 27 vol. per cent; calcium 8.5 mg. per cent. The spinal fluid, the day after admission, showed an increased pressure, but was otherwise normal in every respect. A roentgen-ray of the lungs revealed no pathologic process.

The day after admission the child became comatose; signs of meningeal irritation developed; carpopedal spasm was noted, as well as paresis of the left side of the face with unequal pupils. The edema of the eyelids became more marked. The temperature ranged from 105° to 106° for 36 hours, then began rising and reached 109° at the time of death, which occurred 48 hours after admission or four days after the beginning of the illness. The final clinical diagnoses were: toxic nephritis; meningismus; acidosis; (?) septicemia.

Autopsy was entirely negative grossly except for edema of the brain. Blood culture was known to be sterile up to the time of the autopsy. As a last resort in attempting to explain the illness and death, one of the clinicians asked the pathologist to take a piece of the diaphragm for microscopic study. This was a most fortunate inspiration, as the cause of death would otherwise probably never have been known. Unencysted larvae of *Trichinella spiralis* were found in the diaphragm. The heart showed a moderate leukocytic infiltration. The brain showed congestion of all vessels, but no trichinae were seen and there was no evidence of an encephalitis, in spite of the clinical picture. This patient seems to have had the shortest clinical course with positive autopsy findings on record, at least in the literature of the past 25 years.

Case 3. "Mumps."

A 14 year old female. Two weeks before admission the patient developed bilateral parotid swellings, thought by the family to be due to mumps. She also had diarrhea, lasting two days, and fever of 102° to 103° up to the day of admission, when it rose to 105°. There were vague pains in the legs, and for the past four days intermittent epigastric pain. A four year old sister (case 2) had died two days previously, but the results of the microscopic sections were not known when this patient was admitted. A four year old brother was said to be at home with fever and puffy eyelids. Physical examination: temperature 105°; pulse 116; respirations normal. The child looked acutely ill. The liver and spleen were slightly enlarged; there was questionable swelling of the eyelids and over the parotid glands, and very slight tenderness of the leg muscles. The admission diagnosis was: 1. Mumps—convalescent (?); 2. Trichiniasis (?). The leukocyte count was 6,000 with 76 per cent polymorphonuclears (of which 49 were immature), 11 per cent lymphocytes, and 13 per cent eosinophiles. The blood was negative for trichina larvae (Herrick-Janeway method). The eosinophilia increased to 40 per cent five days later and decreased to 14 per cent in another seven days. The temperature fell gradually, reaching normal on the eighth day in the hospital. Biopsy, done on the twenty-third day of illness, was positive. The "parotid swelling" was probably caused by an edema of the masseter muscles.

Case 4. "Renal colic."

A 35 year old female. Two weeks before admission the patient noted a swelling of the face and neck, a puffiness of the eyelids, a stiff neck, and fever. Except for the fever, these symptoms disappeared in eight days. Five days before admission she developed severe pain in the left flank, which had persisted. There was no radiation of the pain, and it was severe enough to require morphine. Severe frontal headache and occasional diplopia were present during the illness. On examination the patient

was found to be in very severe pain. The spleen was felt at the costal margin. There was tenderness, seemingly in the muscles, over McBurney's point and in the left lower quadrant. Tenderness was noted over the calf and buttock muscles and in the left costovertebral angle. The admission diagnosis was: renal calculus. The blood count, done subsequent to the diagnosis, showed a total count of 14,700 leukocytes with 49 per cent polymorphonuclears (of which 22 were immature), 22 per cent lymphocytes, and 29 per cent eosinophiles. The temperature never rose above 101.6° in the hospital. After the first blood count, the diagnosis was changed to trichiniasis, and biopsy several days later was positive. If more attention had been paid to the history and if trichiniasis had only been thought of, the diagnosis should have been apparent on admission, even before seeing the result of the blood count.

Case 5. "Typhoid fever."

A 6 year old female. History of three days of fever, abdominal pain, and puffy eyelids. Positive findings on physical examination: edematous eyelids and a palpable spleen. The admission diagnosis was: Pyelocystitis. The leukocyte count was 4,400 with 34 per cent polymorphonuclears, 54 per cent lymphocytes, and 12 per cent eosinophiles. Unfortunately no further counts were done. The Widal test was positive in dilutions of 1:40 and 1:80, but higher dilutions were not carried out, and the test was not repeated. The blood, urine, and feces were all negative for typhoid bacilli on culture.

The temperature fluctuated between 99° and 103° during the first week in the hospital; then during the next six weeks it fluctuated from subnormal (97° to 98°) up to 100°, with a rise to 101°–103° about once weekly. The pulse was always disproportionately high. A diagnosis of typhoid fever was made, and the chart signed out as such. Against this diagnosis are the following: an eosinophilia, a relatively low temperature lasting only 12 days, a rapid pulse, absence of rose spots, negative cultures of the blood, stools, and urine. The Widal test was done when the temperature was high, was not carried to dilutions higher than 1:80, and was not repeated. In favor of the diagnosis of trichiniasis are the history and observation of puffy eyelids. The fever, enlarged spleen, leukopenia, and positive Widal test would fit either diagnosis. The eosinophilia, even though only 12 per cent, rules out typhoid and clinches the diagnosis of trichiniasis in this case.

This patient returned to the hospital four years later at the age of ten. The history was of one day's duration with fever, pain in the muscles, pain and burning in the eyes, and headache. Examination revealed tenderness in various muscles and slight puffiness of the eyelids. There was an eosinophilia of 30 per cent, and further questioning brought out the fact that she remembered having eaten pork six weeks previously (although the pork which caused her symptoms was undoubtedly eaten subsequently). Biopsy was reported as negative; but muscle taken from her sister, a patient at the same time, contained the trichinae. The diagnosis of trichiniasis appears entirely justified in view of the history, the physical examination, the eosinophilia, and the sister's positive biopsy. This case illustrates the occurrence of reinfection in this disease, which, although rare, certainly does occur.

Case 6. "Nephritis."

A 10 year old female. Present illness: puffiness of the face for two days. Past history: "kidney trouble" at the age of two years. Physical examination: edema of eyelids; congested pharynx; systolic murmur at apex; temperature 102°. Admission diagnosis: Acute nephritis. Blood count the next day showed 40 per cent eosinophiles; biopsy was positive; urine was normal. Final diagnosis: Trichiniasis.

Case 7. "Grippe."

A 9 year old female. History of 36 hours of pain in the eyes, coryza, cough, headache, generalized body aches, fever, and puffy eyelids. Examination revealed edema of the eyelids, crepitant râles over the left lower lobe, tenderness of the muscles of the neck and legs; temperature 103°. The admission diagnosis was: grippe or broncho-

pneumonia. The first blood count, done subsequent to this diagnosis, showed 10,000 leukocytes with 63 per cent polymorphonuclears (of which 50 were immature), 31 per cent lymphocytes, and 6 per cent eosinophiles. Course: the temperature ranged from 102° to 104° for nine days with one spike to 106°. Eosinophilia later increased to 36 per cent and biopsy was positive.

Case 8. Accidental finding—time of infestation not known.

A 39 year old female. Admitted to the hospital with a fracture of the femur. An open reduction was done, and bone from the femur with some of the surrounding tissue was sent to the laboratory for routine examination. The pathologist's report was as follows: "Extremely sclerotic and degenerated voluntary muscle. Tissues show focal and perivascular round and plasma cell infiltration. They contain several encapsulated trichina larvae. Diagnosis: Trichiniasis."

Blood smears taken subsequently on two occasions showed 0 and 2 per cent eosinophiles. No history suggestive of trichinous infection could be elicited, and it is reasonable to assume that it occurred many years before.

Case 9. No symptoms or signs.

A 9 year old female. The mother of this child was a patient in the hospital with typical history and physical findings of trichiniasis and an eosinophilia of 61 per cent. This child had no symptoms or signs whatever, and yet was found to have an eosinophilia of 40 per cent, which decreased after 4½ months to 10 per cent. This case illustrates the fact that if one will investigate the members of the family of patients with trichiniasis, one will discover many more instances of the disease, either unrecognized or misdiagnosed.

Case 10. "Acute sinusitis."

A 9 year old male. Admitted on January 7, 1938. History: Two days of puffy eyelids, generalized abdominal pain, slight, non-productive cough, and fever up to 104°. Examination: Child looked acutely ill; temperature 103.8°; pulse 88; respirations 22. There was edema of the eyelids; the sinuses transilluminated poorly; the spleen was palpable with a very tender edge. Admission diagnosis: Acute pansinusitis. Roentgen-ray examinations: normal lungs; sinuses "fairly clear." Urine normal on several occasions. Sedimentation rate was within normal limits, even while patient had a high temperature. Blood culture and Widal test: both negative on two occasions. Blood counts were as follows:

1/7	: WBC	13,100;	polys.	75%	(21	immat.);	lymphs.	22%;	eosinos.	3%
1/10	: "	15,150;	"	73%	(14	");	"	24%;	"	3%
1/20	: "	9,650;	"	64%	(15	");	"	36%;	"	0%
1/26	: "	——;	"	58%	(18	");	"	25%;	"	17%
1/27	: "	9,200;	"	45%	(6	");	"	33%;	"	22%

I believe that the eosinophilia was probably missed during the first two weeks of hospitalization because of technical errors. The smear which showed 17 per cent eosinophiles had been stained with MacMeal's tetrachrome stain, whereas another smear taken at the same time, but stained with the Wright's stain then in routine use, showed no cells with granules red enough to allow the cells to be identified as eosinophiles with assurance. This has happened on several occasions to my knowledge, and it may account for some of the cases in the literature with a low or absent eosinophilia.

After the patient's temperature had varied from 102.0° to 105.4° for four days in the hospital, it gradually fell to normal. The temperature-pulse curve resembled that of typhoid, which was strongly suspected at first. For a while the muscles were so tender that the child could scarcely move because of pain. Biopsy taken four weeks after the onset of the illness was positive for trichinae. Additional questioning brought out the fact that one week before the onset, the family had eaten some smoked ham without further cooking. The father had had muscle pains, diarrhea, and fever at home, and was later found to have 39 per cent eosinophiles.

Case 11. "Fever of unknown origin."

A 40 year old female (mother of case 10). Admitted December 30, 1937. For 10 days before admission this patient had had high fever, up to 104.0°. Sweating and chills were prominent. Headache and generalized body aches and dull abdominal cramps with constipation were present. She vomited once the day before admission. Family history: her husband was ill at home with chills and fever. On examination she looked acutely ill; there was pallor and the tongue was coated. The temperature was 103.6°; pulse 100; respirations 26; blood pressure 92 systolic and 68 diastolic. The spleen was not felt. There was no muscle tenderness and no lymphadenopathy. The rest of the examination was also negative. On admission the diagnosis was deferred.

Blood studies showed the following: on admission, the leukocyte count was 18,000 with 76 per cent polymorphonuclears (of which 28 were immature); 22 per cent lymphocytes; 2 per cent eosinophiles. Four days later the leukocyte count was 18,350 with 90 per cent polymorphonuclears (of which 27 were immature); 9 per cent lymphocytes; 1 per cent eosinophiles. Laboratory examinations, including cultures of the blood, urine, feces, and agglutination tests for typhoid, paratyphoid, and undulant fever, were all negative. Roentgen-rays of the lungs showed no lesions. Course: the temperature fluctuated between 99.0° and 105.6° for six days, and then stayed below 100°; the pulse varied from 88 to 96, which was low compared to the temperature. Physical examination continued to be essentially negative. The patient was discharged after 15 days in the hospital. The final diagnosis was: "Fever of Unknown Origin."

She returned 10 days later with a history of having had diarrhea (5 to 10 stools daily), starting just after leaving the hospital. She did not think she had had fever, but the temperature had not been taken. There were no chills or other symptoms. Examination was essentially negative again. The diarrhea continued for four days. The temperature was normal. The various agglutination tests were again negative. The blood counts were as follows:

1/23: WBC 13,500; polys. 39% (3 immature); lymphs. 37%; eosinos. 24%.
1/26: WBC ——; " 76% (4 "); " 24%; " 0.
1/26: (later same day using tetrachrome stain): Eosinophiles: 33%.
2/4: WBC 17,100; polys. 43%; lymphs. 20%; eosinos. 37% (after 2 weeks of normal temperature).

Biopsy done seven weeks after onset of the original symptoms was positive.

Comment: Here again I feel that the eosinophilia was overlooked because of a poor Wright's stain, at least on the examination of 1/26, on which date another smear stained with MacMeal's tetrachrome stain showed 33 per cent eosinophiles. Whether or not the patient actually had more than the 2 per cent eosinophiles recorded on the first admission is a moot question, but I am inclined to believe that she did.

Case 12. "Encephalitis" or "Chorea and Rheumatic Heart Disease."

A 32 year old housewife. Admitted with a history of two weeks' dry cough, with soreness of the abdominal muscles, which she attributed to the strain of coughing. For a period of five days about a week before admission she had had 5 to 6 watery, brown stools, without blood or mucus, daily. Palpitations were noted for the past 10 days. Loss of power of the right hand and arm was a prominent symptom during the past week, and pain and tenderness of the finger tips of both hands for the past few days. During the two days prior to hospitalization she noted a failing memory and a lack of power of concentration. Past history: Appendectomy at 17 years; articular rheumatism seven years before at the age of 25; tonsillectomy at 27. On examination she presented the following picture: temperature 101.6°; pulse 108; respirations normal. She appeared acutely ill and pale. There were athetoid movements of the head, arms, and legs. A loud systolic murmur was heard at the

apex and at the base. The blood pressure was 118 systolic and 88 diastolic. The cardiac rhythm was regular. The reflexes were normal except for the absence of the abdominals. There was an inability to coördinate. The admission diagnosis was: Encephalitis or chorea with active rheumatic heart disease. The leukocyte count was 18,500 with 80 per cent polymorphonuclears (28 immature), 18 per cent lymphocytes, 2 per cent basophiles, 0 eosinophiles. The sedimentation rate was moderately increased. The Wassermann test was negative, as were several urine examinations. Roentgen-ray of the lungs revealed no lesions. The spinal fluid was under no increased pressure, was clear and had 10 leukocytes and 50 erythrocytes per cubic millimeter; the protein was 53 and the sugar 69 mg. per cent. Wassermann and colloidal gold curve were negative. An electrocardiogram on admission showed a rate of 83; PR: 0.22; QRS: 0.08. Lead I: S slurred and notched; T low. Lead II: T diphasic. Lead III: T inverted. Later tracings showed a gradual return to normal, but with constant inversion of T in Leads II and III.

Course: The temperature varied from 99.0° to 101.0° for 10 days; then it remained normal. Three days after admission a neurological consultation was recorded as follows: "Paralysis of convergence and accommodation; right cerebellar asynergia; absent abdominals; mental torpor; bilateral papilledema. Diagnosis: Encephalities of unknown etiology." The patient needed catheterization for a number of days. There was a gradual improvement in the general condition, although the ocular signs remained. After 10 days in the hospital a repeat blood count, the first since the admission count, showed 50 per cent eosinophiles, and four days later there were 51 per cent. After the eosinophilia was discovered, the etiology of the encephalitis and myocarditis was clear. Close questioning brought out the fact that the patient had had puffiness of the eyelids during the first few days of the illness. Search of the blood and spinal fluid 34 days after the onset of symptoms failed to reveal any larvae. Biopsy performed the next day was positive. The patient was discharged on the twenty-second hospital day after considerable improvement. The combination of encephalitis and myocarditis is not extremely rare [29, 30, 42]; but the prognosis is poor. This patient was seen eight months later. She had made a complete recovery except for slight residual weakness of the right arm and leg. The eosinophiles were only 3 per cent; i.e., within normal limits.

It is interesting to note that in practically all the misdiagnosed cases recorded above, there was one clue, which if heeded, would have suggested the correct diagnosis; i.e., a history of *puffy eyelids* in the patient or in a member of the immediate family, or an *edema of the eyelids* noted during the physical examination. Sometimes the history of puffy eyelids was not obtained until after the diagnosis had been made, but most often the physician paid no attention to that aspect of the history or attributed it to some other condition. I should like to suggest that in taking the history in all acute illnesses, specific inquiry be made routinely concerning the presence of puffy eyelids; and if there is such a history or observation on examination, that the diagnosis of trichiniasis be seriously considered.

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DIFFUSE PRIMARY TUBERCULOUS ENTEROCOLITIS; A REPORT OF TWO CASES *

By H. L. Bockus, M.D., F.A.C.P., H. Tumen, M.D., and K. Kornbloom, M.D., *Philadelphia, Pennsylvania*

Diffuse ulcerative tuberculosis of the intestines not associated with pulmonary tuberculosis is extremely rare, particularly in the United States. The subject is inadequately treated or completely ignored in most American textbooks and systems of medicine. For these reasons it was deemed advisable to report our experience with two cases, unique because of the extent of intestinal involvement and complete roentgenologic data. A review of the literature is included.

Review of the Literature

In 1902 Heller [1] stated that the primary focus of the infection was intestinal in 30.6 per cent of tuberculous children. Edens [2] reported in 1905 that the initial focus was "abdominal" in 25 of 176 patients with tuberculosis. Beitzke [3] found 13 cases of primary intestinal involvement in 1100 autopsies. Eight of these were children and five were adults. In 1908 Fischer [4] reported three cases of what he considered primary bowel tuberculosis in adults. Hamburg,[5] on the other hand, failed to find a single instance of that type in 335 necropsies on children with tuberculosis. These older reports are difficult to evaluate because the pathologic nature of the primary complex was not fully understood prior to the studies of Ghon and of Ranke. Infection was frequently referred to as "abdominal" in origin with no attempt to segregate cases with ulcerative lesions in the bowel from those with only mesenteric gland disease.

Among other studies that may be quoted are those of Wollstein,[6] who reported six instances of tuberculosis of undoubted intestinal origin in 185 autopsies on tuberculous children. Later, with Spence,[7] she noted an incidence of 4.8 per cent of "primary abdominal involvement in 184 cases of childhood tuberculosis." Canti [8] stated that of 16 children with Koch infection, one had primary ulcers in the ileum. Opie [9] discovered no instance of healed mesenteric gland tuberculosis in 93 children and 50 adults living in St. Louis but did find such a condition in 18 of 66 British soldiers. Schurmann [10] reported that in 784 cases with a single primary complex in the lymph glands, this was abdominal in 102 or 13 per cent. Siegmund [11] stated that tuberculosis originated in the bowel in 3 to 4 per cent of all those infected. Scott [12] found 32 (10.6 per cent) primary abdominal infections

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From the Gastroenterologic Division of Internal Medicine, Graduate Hospital of the University of Pennsylvania.

among 300 Chinese dying of the disease. Blacklock [13] made a survey of 1800 consecutive autopsies on Glasgow children and found 283 to be tuberculous, the original focus being abdominal in 101 or 35.7 per cent of these. Iizuka [14] found evidence of a primary bowel lesion in 101 or 4.4 per cent of 2500 cases of Koch's disease. Maxwell [15] reviewed the autopsy findings of 233 cases of intestinal tuberculosis and reported 181 to be of the ulcerative type, among them being 15 cases (nine in children and six in adults) which were apparently "primary." Comessatti [16] found that in 159 instances of intestinal tuberculosis all but five were associated with pulmonary infection. The studies of Opie [9] and of Blacklock [13] as well as the earlier findings of Still (quoted by Wollstein [6]) call attention to the relatively high incidence of primary abdominal tuberculosis in the British Isles.

It should be noted that these reports were based upon necropsy findings in which the presence of characteristic changes in the mesenteric lymph glands was looked upon as evidence of the onset of the tuberculous infection in the bowel and that actual intestinal ulceration was found in only a few of the cases cited. Thus, of the 25 cases reported by Edens [2] only five revealed disease of the bowel wall itself at the time of death. Intestinal ulceration was encountered in only three of the 13 instances of primary intestinal tuberculosis described by Beitzke.[3] Fifty-seven of the 102 patients studied by Schurmann [10] had only mesenteric gland involvement. Intestinal ulcers were seen by Scott [12] in only three of his patients, who ranged in age from 10 months to 7 years. Blacklock [13] noted that in only 18 cases in his series was there naked-eye evidence of bowel ulceration—all of these being in children under five years of age. Even when ulceration was present, it was usually not very striking and involved only a relatively small area of the intestine. Iizuka [14] expressed the opinion that the visceral component of a primary intestinal lesion, that is, the bowel ulceration, has such marked tendency to prompt healing that it may be difficult to find macroscopically. In this connection, the work of Medlar and Sasano [17] may also be cited. They inoculated eight guinea pigs subcutaneously with tubercle bacilli. Serial sections of the lymphoid tissue in the bowel demonstrated tuberculous lesions and organisms in every case; yet only one showed a typically tuberculous bowel ulcer. The initial intestinal lesion seemed to occur in those intestinal glands which dipped deeper into the lymphoid tissue. From this point lesions were set up in the adjacent submucosa. The overlying mucosa might slough off and leave an ulcer but in many instances it remained intact, so that grossly discernible lesions did not occur in the bowel. The mesenteric lymph nodes were invariably infected. Such observations indicate that an initial lesion in the bowel wall may not be accompanied by obvious ulceration. Most workers are agreed that if the mesenteric nodes show evidence of primary tuberculosis, the original lesion occurred in the intestinal wall. The intestinal lesion may be easily overlooked, as Ferris [18] has demonstrated.

In addition to the statistical studies mentioned above, the literature contains reports of isolated cases of primary intestinal tuberculosis of the ulcera-

tive type. One of the most important of these is that of Reichle,[19] who reported an apparently primary tuberculous infection of a small segment of the distal ileum with caseous necrosis of adjacent lymph nodes in a boy eight years of age. In the same paper he included a brief description of an additional patient who may have had a primary intestinal complex. Pitts [20] reported the cases of two children of 11 and 2 years of age. The first had a few small tubercles in the lower jejunum with involvement of the mesenteric glands. The second had a tuberculous ulcer of the jejunum and caseation of the abdominal lymph nodes. In neither case was any additional focus of the infection discovered outside of the abdomen. Single cases of more extensive and apparently primary ulcerative intestinal tuberculosis have been recorded by Dixon and Beaver [21] and by Mourier.[22] The former presented the clinical and autopsy findings in a woman, 21 years of age, in whom the disease process involved the terminal 30 cm. of the ileum as well as the cecum and 12 cm. of the ascending colon. The latter reported finding very striking ulceration in the ileum, cecum and descending colon of a girl 17 years of age. In neither of these were roentgen-ray studies carried out during life. Schapiro [23] described the case of a man of 30 years of age with an extensive stenotic lesion of the mid-portion of the small bowel, which was resected with good results. The resected portion of the bowel and its adjacent lymph nodes showed changes highly suggestive of tuberculosis but acid-fast organisms were not found. Riche, Lonjon and Joyeux [24] also reported as an example of primary intestinal tuberculosis a patient with multiple stenotic areas in the ileum and infiltration of the cecum. The published description, however, leaves some doubt as to the exact etiology of the changes found and this may have been another instance of non-specific ileitis.

On the basis of roentgen findings, Pigorini [25] diagnosed primary tuberculosis of the upper small bowel in a patient 38 years of age. His report, however, contains no substantiating bacteriologic or pathologic studies. Colombo [26] reported the case of a man of 39 years of age, who showed roentgenographically a jejunal deformity and what seemed to be the result of pressure of a mass on the stomach and on the colon. Operation revealed an infiltrating lesion of the jejunum and a diagnosis of tuberculosis was made because of the gross appearance of the lesion. Neither biopsy nor bacteriologic studies were performed.

Investigations undertaken to determine the strain of tubercle bacillus responsible for primary intestinal tuberculosis indicate a preponderance of infection by the bovine type. This was true of 70 per cent of the patients studied by Siegmund [11] and of 9 of the 11 cases in Blacklock's series in which bacteriologic work was done. Mourier [22] found this variety of organism in the case reported by him and it was probably present in Reichle's [19] patient. This frequent isolation of the bovine strain is looked upon as evidence that the disease is often contracted by ingestion of raw milk from infected cows—a condition thought to exist more widely in England and Scot-

land than in this country. Giovanardi,[27] however, was able to produce intestinal tuberculosis in rabbits by feeding both the human and bovine strains of bacilli.

Case Reports

This report is concerned with a description of 2 cases of extensive primary enterocolic tuberculosis.

Case 1. M. L., a 15 year old Slavish boy, born in Philadelphia, was admitted to the Graduate Hospital, June 24, 1935, complaining of severe abdominal pain, diarrhea, fever and weakness. His father gave a history of childhood tuberculosis. The boy had been admitted to a neighboring hospital in 1929 and again in 1930 and was stated to have had either recurring acute appendicitis or, possibly, abdominal lymphadenitis. No gastrointestinal examinations were made at that time. It was learned that since 1929 the boy had complained of bouts of slight abdominal discomfort at very infrequent intervals. In April 1935, two months prior to admission, moderately severe crampy pains developed. They were usually postprandial and not definitely localized. They gradually increased in severity and frequency and were associated with marked borborygmi and the development of sausage-like masses which the patient could palpate. Diarrhea began three weeks before admission, and the boy averaged eight watery stools daily during this time. Defecation did not relieve the pain. Blood, mucus and pus were not noted in the stools. Fifteen pounds were lost after the onset of these symptoms. There were no pulmonary symptoms.

On admission the patient was pale and emaciated. He appeared toxic and had a moderate afternoon fever. The chest examination was negative. The abdomen was moderately distended, but there was no evidence of ascites. At least three distinct sausage-shaped, tender abdominal masses were palpated. They were located in the upper left quadrant, lower midepigastrium and lower right quadrant. Other less prominent bowel segments were also felt. The ability to feel these tumors subsequently depended on the state of distention of the abdomen and the degree of tenderness and muscle guarding. They gave the impression of thickened, inflamed bowel segments. Rectal examination suggested some thickening of the rectal wall in the region of the first Houston valve. Proctosigmoidoscopy tended to rule out ordinary ulcerative colitis since there was no evidence of a diffuse inflammatory process of the mucosa. There was, however, an irregular granulating ulcerative area of inflammation, 3.5 centimeters in its transverse diameter and 1.5 centimeters longitudinally, on the right anterior wall of the rectum above the first Houston valve. This had overhanging edges and resembled an amebic ulcer. Scrapings and smears from these areas yielded no acid-fast organisms or amebae.

Tubercle bacilli were not recovered from the urine. The erythrocyte count was 2,900,000 with 7.5 grams per cent of hemoglobin and 6,300 leukocytes with a normal differential and no increase in young granulocytes. The Wassermann reaction was negative. Repeated examinations of the feces failed to demonstrate amebae. Dysentery and typhoid organisms could not be recovered by culture. Large numbers of the tubercle bacilli were found in six of the seven stools which were examined. A guinea pig, inoculated with a fecal emulsion, developed tubercles in the liver and spleen. The tubercle bacilli studied by Dr. Fred Boerner were believed to be the human strain. The tuberculin test was negative with precipitated tuberculin. The sedimentation rate was 54. The blood chemistry was normal except for moderate hypoproteinemia. Many of the stools were positive for occult blood.

Roentgenological examination was of great interest. The chest was examined twice and showed no evidence of parenchymal disease (figure 1). A preliminary plain film of the abdomen showed several very small calcified lymph nodes in the upper abdomen on both sides. Barium enema revealed an appearance of the colon characteristic of advanced ulcerative colitis with involvement from the cecum to the

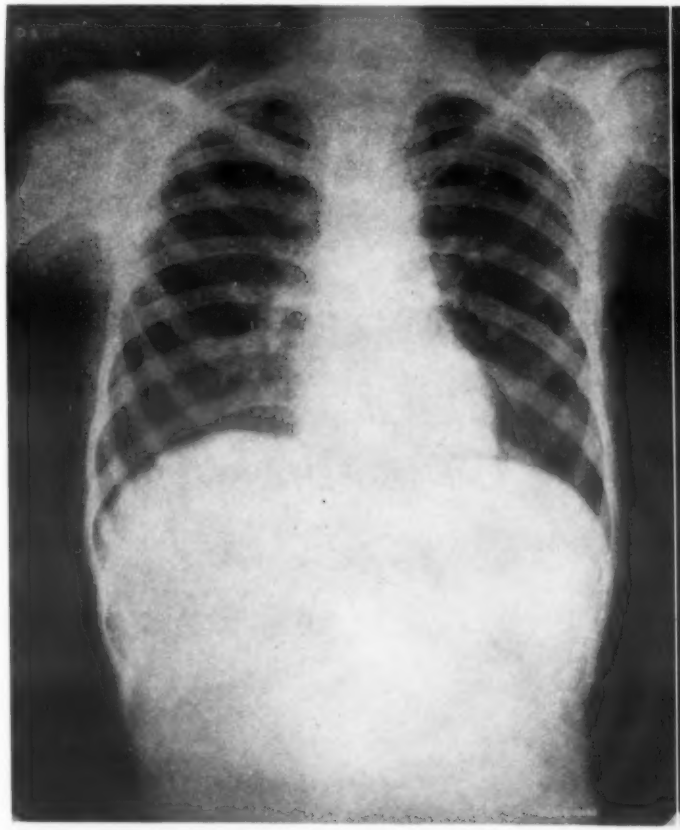

FIG. 1. (Case 1) The chest is negative for pulmonary tuberculosis.

FIG. 2A. (Case 1) Barium enema study of the colon presenting the characteristics of an extensive and fulminating colitis. Before evacuation.

FIG. 2C. Double contrast enema. Note the disturbance in the mucosal pattern.

FIG. 2B. After evacuation.

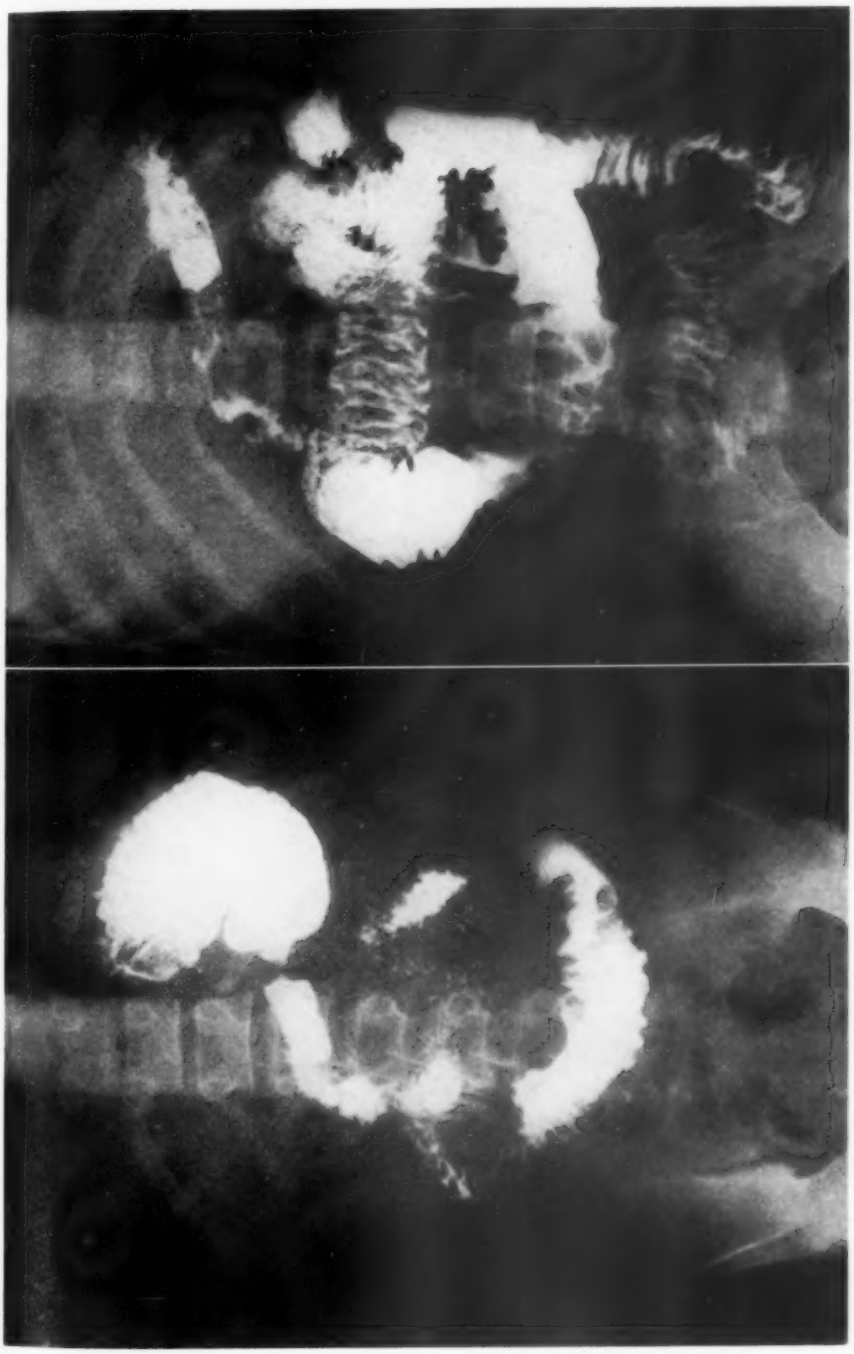

FIG. 3A. (Case 1) Primary tuberculous enterocolitis. Stomach, duodenum and proximal jejunum.

FIG. 3B. Taken one hour after figure 3A.

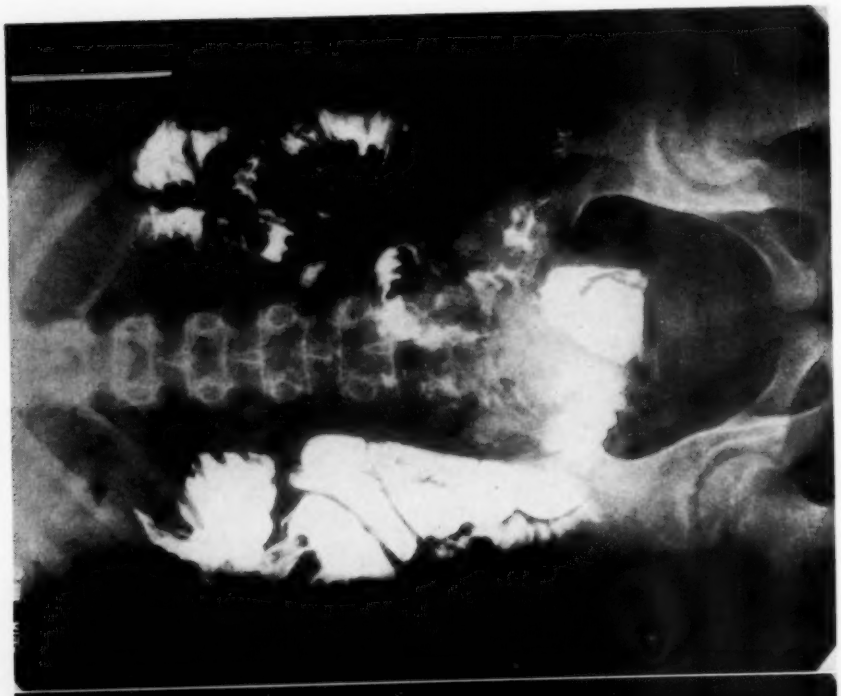

FIG. 3D. At six hours the meal has not yet reached the cecum.

FIG. 3C. Taken two hours after figure 3A; extensive changes in the small intestine.

sigmoid. There was considerable spasticity and irritability with shortening and narrowing of the colon and a lack of haustral markings. In addition, the silhouette of the colonic borders had a serrated, fuzzy appearance which we have frequently seen in the more acute fulminating types of colitis. The contents rushed into the loop of terminal ileum and showed definite dilatation of this portion of the small intestine (figures 2, 2B and 2E).

In the study of the upper gastrointestinal tract (figure 3) evidence of pathology became apparent as soon as the duodenum was reached. The duodenum distal to the cap was considerably dilated and showed an exaggeration of the mucosal rugae. This was found subsequently to be characteristic of the entire small intestine, the alteration being, however, definitely more marked in the jejunum and upper ileum. Some of the dilated loops were larger than a normal colon (figure 3B). While there were a few points of narrowing, dilatation of the bowel dominated the picture. The serrated appearance of the mucosal folds was a striking feature (figure 3C). Where this was absent the bowel wall presented a somewhat rigid appearance in spite of the dilated condition. The gastric motility was increased, while small intestinal motility was definitely delayed (figure 3D). Small patchy areas of the small bowel showed hyperperistalsis but in the dilated loops there was a definite stasis. The impression was obtained that the jejunum and upper ileum were more involved than the lower ileum. After reaching the colon, the opaque meal passed rapidly along into the descending colon (figure 3E). The appearance of the colon was essentially the same as found by barium enema examination.

Treatment consisted of a smooth, high caloric, vitamin rich diet, vitamin concentrates, calcium, iron, kaolin, ultraviolet radiation and transfusions. The course was rapidly down-grade. Abdominal pain became continuous and opiates were frequently necessary. The average afternoon temperature was 102°. Repeated examinations of the chest were negative. Symptoms of small bowel obstruction became more obvious. Exploratory operation, performed by Dr. Walter E. Lee, July 20, 1936, showed extensive tuberculous involvement of the entire jejunum and ileum and of the colon down to the sigmoid. The serosa of the entire bowel was studded with tiny tubercles. There were many areas of narrowing throughout the small intestine with dilated segments of bowel between. The parietal peritoneum, liver and spleen were not involved. The mesenteric glands were extensively enlarged and some seemed caseous. Biopsy of one of these showed typical tuberculous changes. Involvement was so extensive that resection or short circuiting could not be attempted. For a few days after operation the clinical situation seemed a little brighter, but a progressively fulminating toxemia developed. Death occurred August 4, 1936.

Autopsy by Dr. Eugene Case revealed a diffuse ulcerative tuberculosis of the large and small intestines. The ascending, transverse and descending portions of the colon showed enormous tuberculous ulcers and very little normal mucosa remained. The walls of the colon were very thick and tubercles protruded through to the serosa. The large bowel was adherent to the spleen and to several loops of small intestine. The proximal two feet of ileum showed the most marked changes in the small intestine. Below this level the ulcers were fewer and more discrete. The distal portion of the ileum showed no mucosal lesions. Many ulcers higher up in the bowel were healed. Miliary tubercles studded the serosa of the small intestines. All of the mesenteric lymph nodes were large and caseous. Miliary tubercles were found in the liver, spleen, kidneys and lungs. There was no primary tuberculous focus in the lungs.

Discussion

It is probable that bowel or mesenteric gland tuberculosis accounted for this boy's admission to a neighboring hospital five and six years before he

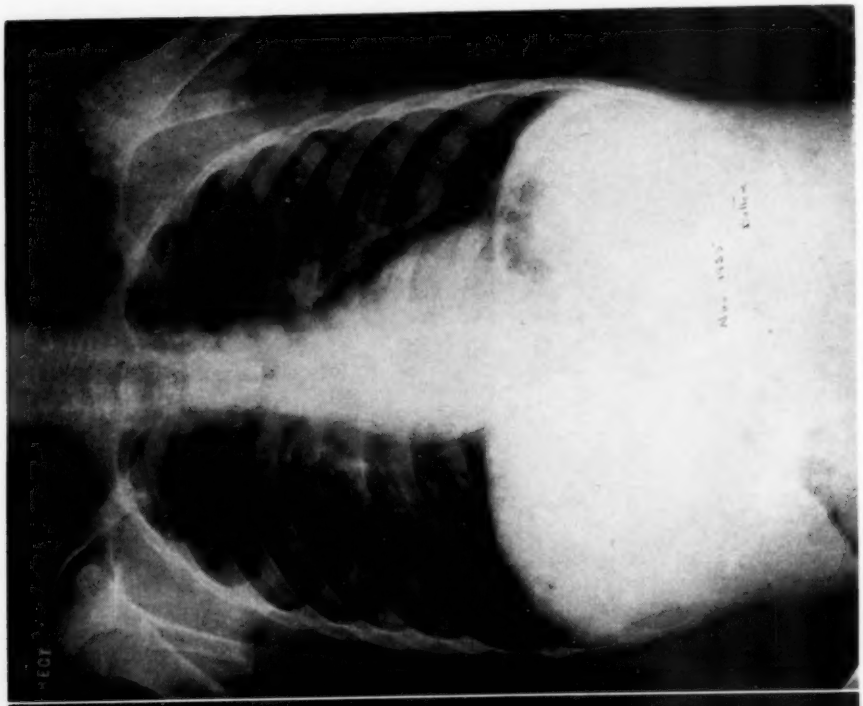

FIG. 4. (Case 2) Repeated examinations of the chest were negative for tuberculosis.

FIG. 3E. At seven hours the involvement of the colon is clearly shown.

was seen by us. There had been very occasional bouts of slight abdominal discomfort since the original attack. The necropsy revealed no evidence of previous appendiceal disease to account for these acute episodes. It is unfortunate that comprehensive studies were not performed at that time, as the disease may have been arrested had intensive therapy been applied. There is every reason to believe that the clinical manifestations of intestinal tuberculosis may be slight and infrequent for months or years and that involvement may be very widespread and of long duration, as it was in this case, before a critical picture is presented. It was obvious at the time of operation that the disease was old and far advanced and that it involved both the intestinal tract and the lymph glands. There was no evidence of miliary tuberculosis at that time. The rapid down-grade course following operation suggested a hematogenous dissemination of the infection by the manipulation which surgery entailed. In this instance the outcome could not have been altered but it is undoubtedly unwise to subject cases with this wide-spread involvement to laparotomy except for the relief of complete obstruction.

The extensive involvement of the colon is most unusual. The lesions were larger and seemed older than those in the small bowel. It is likewise of interest that the terminal ileum was entirely free from ulceration. The roentgenologist had remarked upon the comparative freedom of this part of the bowel from evidence of advanced pathology. The terminal ileum, so rich in lymphatics, is ordinarily the first part of the small intestine to be attacked in intestinal tuberculosis secondary to pulmonary disease.

Case 2. Less than five months following the admission of the first patient, on November 6, 1935, a Jewish boy, J. C., 14 years of age, was admitted to the Graduate Hospital, complaining of slight diarrhea, loss of weight and strength, and malaise. He was born in and always had lived in Philadelphia. We were unable to elicit a history of tuberculosis in the family. The past medical history was of little consequence. It included measles, pertussis, chicken pox, mumps and diphtheria. The initial symptoms of anorexia and weight loss began in September 1934, about 14 months prior to admission. About two months later a tendency toward diarrhea was noted. He passed from four to five soft stools daily. In December 1934, blood-tinged mucus was noted very infrequently in the feces. This situation remained unchanged until March 1935, when the patient was admitted to a neighboring hospital for study. He had lost 15 pounds in weight. After six weeks in the hospital (until May 15, 1935) he gained 10 pounds and the diarrhea disappeared. He was then admitted to a suburban convalescent home in July, where he remained for one month, gaining 10 pounds and becoming symptom-free. The same symptoms recurred in September 1935 and persisted until the time of admission. His general appearance suggested an approximate age of 11 years. There were no indications of adolescence. His nutrition was poor, and he weighed only 75 pounds. There was no edema or ascites. Abdominal examination revealed slight enlargement of both the liver and spleen. The temperature, although usually within normal range, mounted to 101° on several occasions. The erythrocyte count was 3,450,000, the hemoglobin 55 per cent, the leukocytes 7,700 with 60 per cent neutrophiles, 34 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophiles. The nuclear index was 9.0 and the neutrophiles showed some toxic granules. The sedimentation rate was 17 mm. Ag-

glutination tests with all available dysentery strains (Strong, Flexner and Shiga) were negative. The tuberculin test was negative. The only significant change in the blood chemistry was the hypoproteinemia, which the following figures show:

Date	Total Protein	Albumin	Globulin
11/13/35	4.86	3.0	1.86
11/18/35	5.15	3.0	2.15
11/23/35	5.2	2.8	2.40
12/2/35	8.2	3.9	4.3

Twelve stools were examined between November 7 and November 18. Gross blood or mucus was rarely present. The reaction for occult blood was positive only occasionally. Some specimens contained an excessive amount of fatty acid. There were no amebae or other parasites at any time. An acid-fast bacillus, subsequently shown by Dr. Fred Boerner to be a human strain of the tubercle bacillus, was found in three stools passed on different days. Sigmoidoscopy revealed several areas of mucosal hyperplasia surrounding rather small oval ulcerations in the region of the first valve of Houston. The mucosa traumatized easily in this area. The appearance was suggestive of healing amebic ulcerations but it was not quite typical of this. Scrapings from this area failed to show amebae or tubercle bacilli. Cultures from the bowel revealed only strains of colon bacilli. Because of the marked distortion subsequently found in the mucosal pattern of the stomach, somewhat suggestive of a hypertrophic gastritis, a gastroscopy was carried out. The mucosa was stated to be normal. A stained preparation of gastric sediment showed no acid-fast organisms and an inoculation of the sediment into a guinea pig did not induce tuberculosis. Free hydrochloric acid was present in the fasting residuum.

Roentgenological study was of great interest. There was no evidence of disease of the lung parenchyma, although the markings in the hilar regions were somewhat accentuated (figure 4). The stomach films suggested the presence of a hypertrophic gastritis. The duodenal cap was quite large but was never completely filled due to a pressure defect. In the light of the subsequent findings, this was thought to be due to pressure from a mass or enlarged lymph glands. The most striking feature of this part of the examination was the appearance of the small intestine (figure 5). The entire upper small intestine from the upper jejunum for a distance of six or eight feet showed a marked reduction in the size of the lumen (figure 5B). These loops arranged themselves in concentric parallel rings in the left abdomen (figure 5C). The walls of the involved portions of the small bowel appeared rigid and had a serrated contour. The mucosal pattern presented a mosaic appearance. There were various points of constriction throughout the diseased portion of the bowel. The motility of the opaque meal through the small intestine was not markedly disturbed (figure 5D). The cecum was never satisfactorily filled, appearing quite irritable and presenting a ragged outline. At six hours the meal had reached the splenic flexure but a considerable amount remained puddled in the terminal ileum, which was moderately dilated.

The barium enema study (figure 6) in this patient showed less involvement than was found in Case 1. The descending colon showed evidence of considerable irritability, if not rigidity, while the cecum was constricted and spastic. Difficulty was encountered in filling the cecum and none of the contents could be made to enter the terminal ileum.

The findings included a history suggestive of an organic bowel disorder, delay in physical development, fever, malaise, weight loss, palpable enlargement of the liver and spleen, anemia, hypoproteinemia, slight steatorrhea, sigmoidoscopic evidence of a circumscribed ulcerative process at the rectosigmoid, roentgen evidence of extensive disease of the small and possibly of the large bowel and, finally, the recovery

FIG. 5A. (Case 2) Primary tuberculous enterocolitis. Thirty minutes after ingestion of the opaque meal.

FIG. 5B. At two hours marked changes in the small intestine are noted.

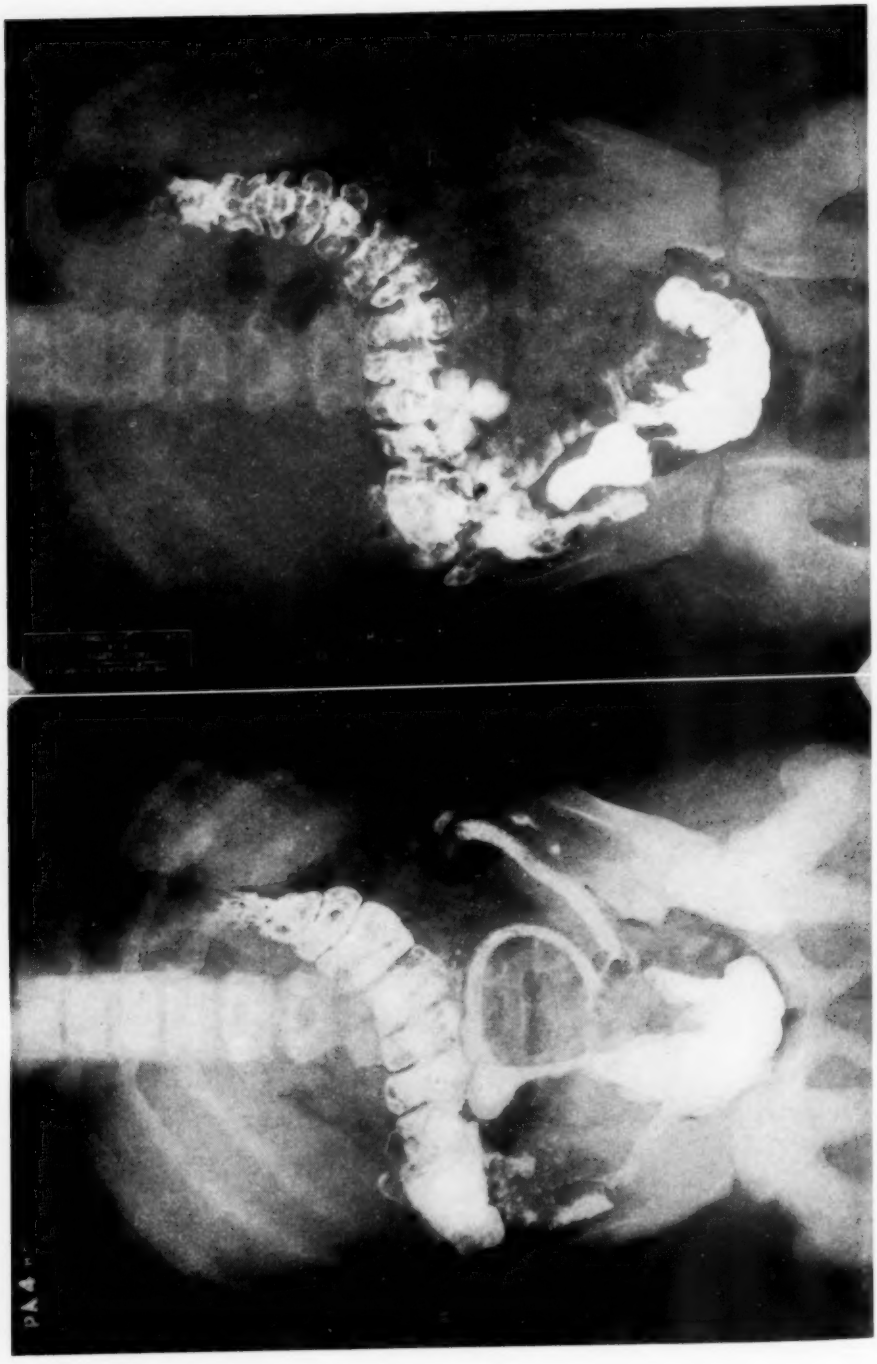

FIG. 5C. At four hours the small bowel involvement is clearly shown.

FIG. 5D. At six hours the meal has reached the splenic flexure. The ileum shows less involvement than the jejunum.

clearly shown.

The ileum shows less involvement than the jejunum.

FIG. 6A. (Case 2) Barium enema study of the colon showing considerable irritability and spasticity.

FIG. 6B. The colon after evacuation and inflation with air.

of the tubercle bacillus in the stools. Because of our previous experience with Case 1 we concluded that we were dealing with a primary enterocolic tuberculosis. Treatment included a highly nutritious diet, ultraviolet radiation, vitamins C, B complex, A and D. Symptomatic improvement was rather rapid: the temperature returned to normal; the diarrhea abated and the blood count improved. The patient was sent to a convalescent home December 10, 1935.

After one month in the convalescent home he was readmitted to the Graduate Hospital for reëxamination. He was then symptom-free but not up to standard weight and strength. Several hyperplastic granular areas were seen in the rectosigmoid on examination through the sigmoidoscope. Although several stools were examined at this time tubercle bacilli were not found. The blood count was normal except for persistent lowering of the hemoglobin. There was no appreciable change in size or consistency of the spleen and liver. The roentgen findings remained the same. The patient seemed in remarkably good condition considering the extensive bowel disease. Follow-up in the Out-Patient Department was uneventful until August 1936, when the stools again became mushy and occasionally blood-streaked and anorexia developed. Admission to the house for study in September revealed no change in the clinical status. The hypochromic anemia was noted again (hgb. 8 gm.). Roentgen findings were similar except for more dilatation of the upper jejunal loops (figure 7A). Roentgenologically it was thought that there had been definite progression of the disease in the small intestine but improvement in the colon. It was now possible to visualize the cecum. More intensive treatment and bed rest caused a remission in symptoms until early in December 1936 when a recurrence of mushy stools, anorexia, weight loss, malaise and anemia (hgb. 8.5 gm.) developed. Readmission on December 12 showed no essential changes in the sigmoidoscopic, physical or roentgen findings. Studies of the blood chemistry again revealed hypoproteinemia but were otherwise normal. Quick symptomatic improvement again followed bed rest and more regular medication and improvement in diet. Calcium, ultraviolet radiation and a high vitamin intake and iron were used throughout the illness. The patient had recurrences of symptoms in April and May of 1937 (figure 7B). These consisted of fatigue and exhaustion and slight diarrhea. He was readmitted to the hospital with each of these episodes and no essential changes were noted in his status except that a border-line positive result was obtained to the Congo Red test, suggesting the possibility of beginning amyloid disease.

The patient was seen regularly in the Out-Patient Department from May 1937 until August 1938. During this time he usually had only one or two fairly normal bowel movements each day and although anorexia was marked and he continued to be emaciated, he complained relatively little. He ate as much as possible of a high-caloric, high-vitamin diet and took vitamin concentrates and iron. The hypoproteinemia and hypochromic anemia persisted. Many stools were examined for acid-fast organisms but none was found. Roentgen-ray survey in January 1938 showed marked mucosal changes similar to those noted before (figure 7C). These changes were particularly marked in the proximal loops of the jejunum, which were seen to be markedly distended and also tubular and stiff. The cecum was well visualized. The chest showed no evidence of tuberculosis.

In August of 1938 it was necessary to re-admit the patient to the ward because of recurrence of diarrhea with seven or eight watery stools daily. The important physical findings at this time were extreme emaciation (the weight had dropped to 65 pounds), pallor, dehydration, slight pretibial edema, marked clubbing of fingers and toes and moderate hepatic enlargement. Another striking feature was the complete lack of sexual development. Sigmoidoscopic examination was performed a number of times during this stay in the hospital, but no definite mucosal disease was noted. A moderately severe hypochromic anemia necessitated continuous iron therapy and a number of transfusions. The plasma proteins ranged from 4.40 to 6.08 gm. per

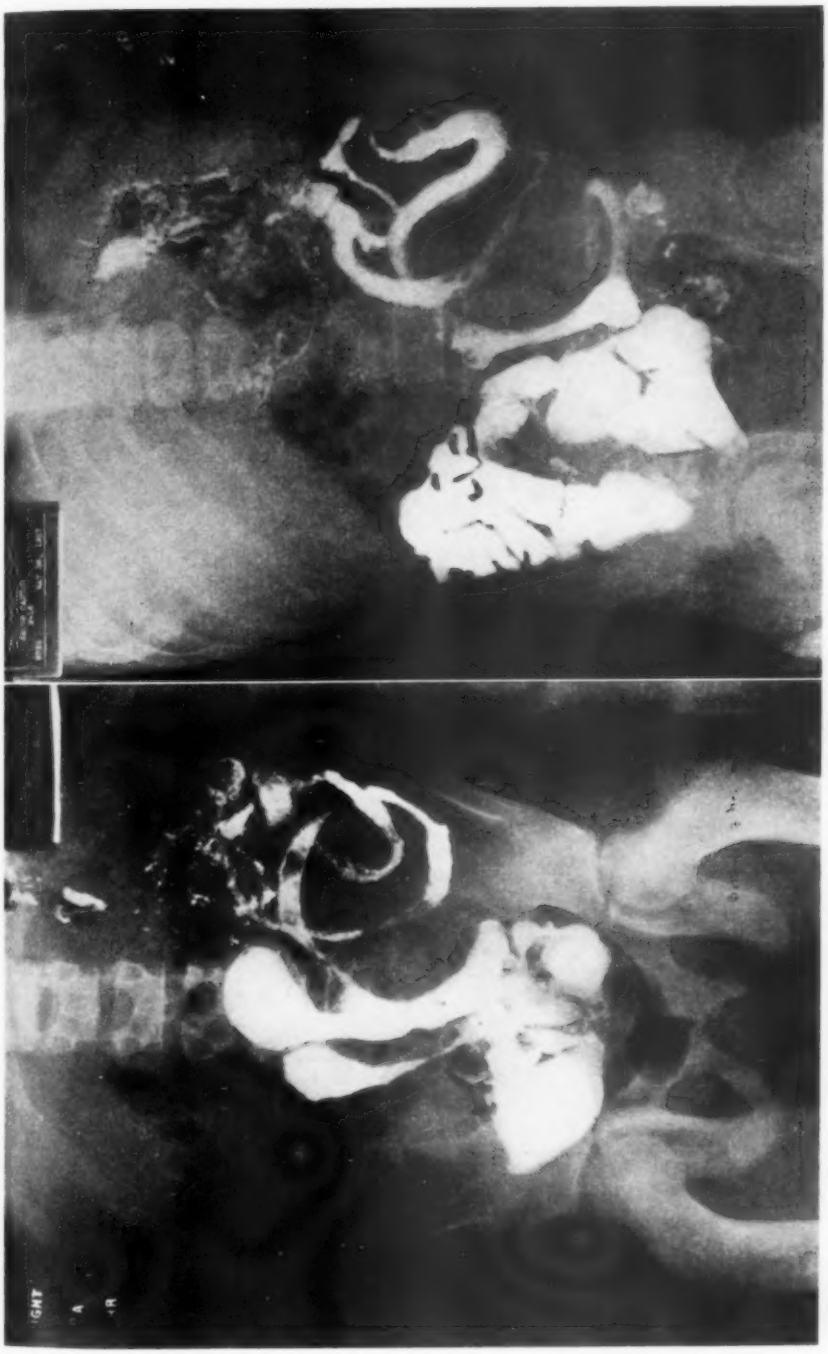

FIG. 7A. (Case 2) Subsequent examinations show the variable but persistent nature of the small intestinal involvement. September 18, 1936.

FIG. 7B. May 26, 1937.

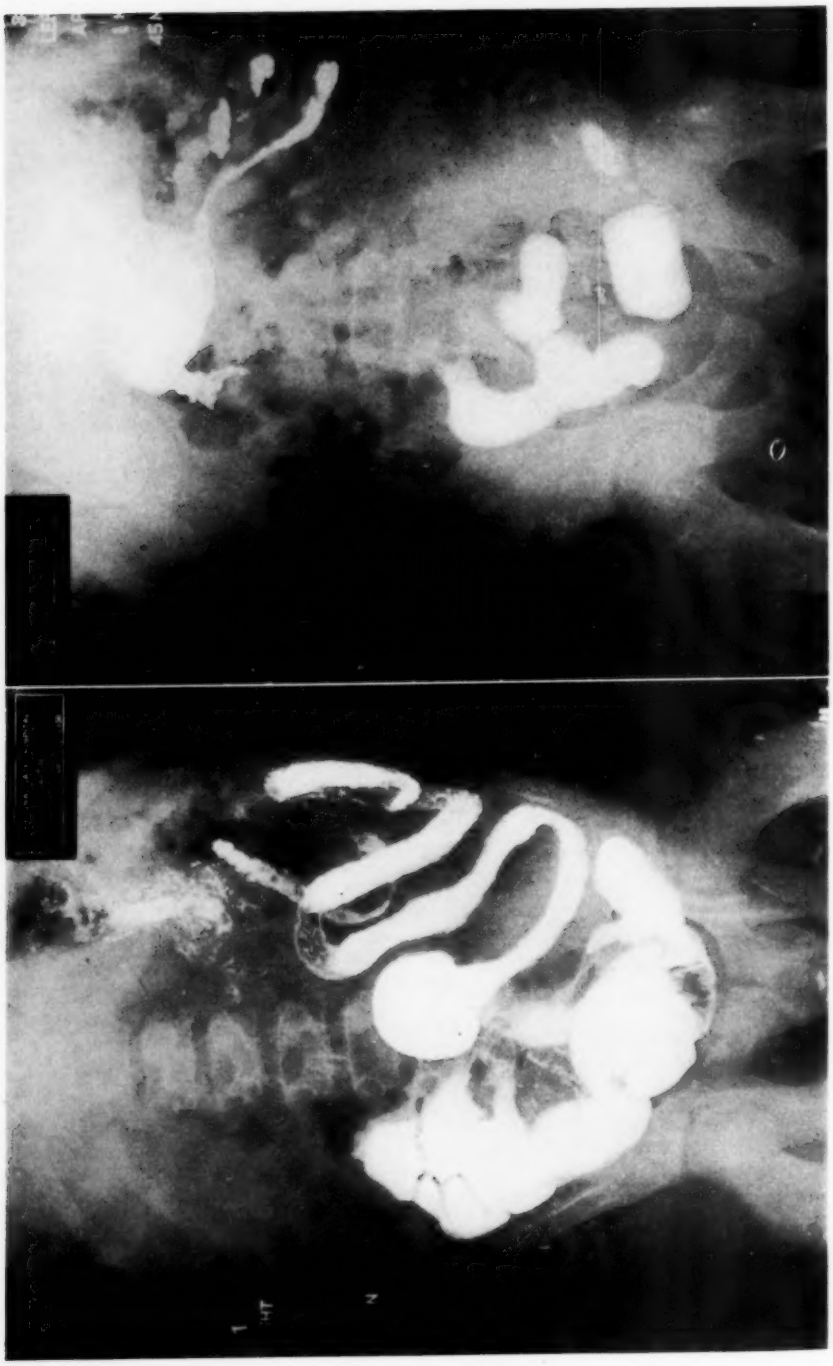

FIG. 7C. January 21, 1938.

FIG. 7D. September 14, 1938. All films in figure 7 were made approximately two hours after ingestion of opaque meal.

cent and the albumin from 2.39 to 3.45 gm. per cent. Transfusions and a high protein diet brought about no appreciable change in the proteins. Tubercle bacilli were not recovered from the stools and guinea pig inoculations failed to induce tuberculosis on this admission. The calcium and phosphorus levels in the blood were normal. A tuberculin test was negative. Roentgen studies showed no evidence of pulmonary tuberculosis. Examination of the epiphyses revealed slight retardation in development. No calcified lymph glands were seen in the abdomen. The changes in the gastrointestinal tract were similar to those previously demonstrated with stiffening and narrowing of the upper small bowel of perhaps a greater degree than at the previous study. The patient remained in the hospital for more than four months. During this time the diarrhea subsided and the blood count improved. There was no gain in weight, however, and on discharge his general condition was about as it had been prior to this most recent exacerbation of his illness.

Discussion

Four years have elapsed since the onset of symptoms and during the past three years this boy has been under our care, coöperating perfectly. He has not matured in any respect and remains extremely weak and on the borderline of complete invalidism in spite of being free of bowel symptoms a large part of the time. Aside from his failure to gain in strength and weight and his delayed puberty, it is remarkable that he is not more miserable with the extensive bowel disease. We have assumed that he has a well defined barrier in the lymphatic apparatus, preventing absorption, and accounting for the persistent anemia, hypoproteinemia and lack of physical development. It seems likely that there are few, if any, sizeable open ulcerations because the reaction for occult blood in the stools was negative usually and because of the failure to recover the tubercle bacilli since the first admission. The lesions at the rectosigmoid have healed completely.

Summary

The literature contains very few instances of primary ulcerative intestinal tuberculosis after the age of eight years. The ages of these boys were 15 and 14 years when admitted. However, the onset may have been at the age of 10 years in the first and at the age of 13 years in the second boy. It was not possible to trace the source of the infection in either case. The milk supply was assumably above suspicion, and there had been no contact with active pulmonary tuberculosis in the household. The bacteriologic studies of Dr. Fred Boerner indicated that the organisms in both cases were of the human strain. There was no evidence of pulmonary tuberculosis past or present in either patient, although M. L. died of miliary tuberculosis after exploration. Their clinical manifestations were dissimilar. M. L. was admitted in a very toxic state with many points of partial bowel obstruction. The second boy was not acutely ill and has developed no signs of obstruction after more than three years of observation. His clinical condition seems almost entirely the result of a nutritional deficiency state, characterized principally by anemia, hypoproteinemia and lack of growth

and development. We are dependent entirely upon the finding of the tubercle bacillus in the stools on the first admission for our clinical diagnosis. This type of case causes one to speculate concerning the possible tuberculous origin of other cases of extensive so-called non-specific enteritis. It is still a moot point whether tuberculous lesions of the bowel may not heal completely, leaving a stenosed bowel segment with blockage of lymphatics predisposing to secondary infection. It is possible that such cases may later masquerade as so-called regional enteritis, although it is most unlikely that many cases of chronic regional ileitis actually started as tuberculosis. It is of interest in this connection that many of the ulcers in the intestine of M. L. were found to be healed at necropsy and there is no reason for feeling that almost complete healing of open ulcers has not occurred in J. C. to account for our failure to recover acid-fast organisms since his first admission and the frequent absence of occult blood in his stools. The roentgen study reveals a bowel silhouette characteristic of the stenosing cicatrizing lesion of regional enteritis except for the extent of involvement.

We have not encountered in the literature a report of primary bowel tuberculosis with such widespread involvement. The distal duodenum, jejunum and upper ileum were completely involved, the terminal ileum being spared in the first case and the last segment to be involved in the second case. No previous report of involvement of the entire colon, such as that present in M. L. has been found in the literature of primary intestinal tuberculosis. In both cases lesions were seen at the rectosigmoid which were undoubtedly tuberculous, although we were unable to recover the organism through the sigmoidoscope.

We have practiced a careful search of many stools for the tubercle bacillus in all patients with ulcerative lesions of the small and large bowel. In cases presenting clinical features suggestive of tuberculosis, stools should be repeatedly examined as organisms may be absent from the stools for considerable periods and present in large numbers at other times. One other feature worthy of comment concerning the stool analysis is the interpretation to be placed upon steatorrhea. A diagnosis of idiopathic steatorrhea is fraught with danger and must never be made until a thorough roentgenologic and bacteriologic survey definitely excludes organic small bowel disease. Steatorrhea is an early and common accompaniment of many types of chronic enteritis, severe enough to disturb motility or intestinal absorption. Naturally it was present in both cases.

No adequate roentgenologic description of primary bowel tuberculosis appears in the literature and certainly there has been no record of cases showing this degree of involvement. Summarizing the roentgen findings in these cases it is seen that the changes occurred in both the large and small bowel. In the small intestine, the disease was characterized by areas of constriction and dilatation. While either of these may predominate it is obvious that constriction is the primary change with dilatation resulting secondarily. Irritability and spasticity of the small bowel seemed not to be

particularly conspicuous, which is in direct contrast to the findings in the colon. Of particular importance is the marked irregularity noted in the outline of the small intestine, indicating mucosal involvement. One case showed a distinct mosaic pattern of the intestinal mucosa. The effect of these changes upon small intestinal motility is variable. In well advanced cases such as here described the changes are quite striking and readily detected. The ordinary gastrointestinal study as customarily conducted would surely detect the condition but a true appreciation of the extent and degree of involvement could be obtained only by a careful and thorough progressmeal study of the small intestine. Such a study would most certainly be required in early cases of lesser involvement.

Conclusion

Two cases of primary tuberculous enterocolitis are reported and the literature reviewed. In both cases the age of onset was later than most cases previously reported. The extent of involvement was noteworthy. A mixed nutritional deficiency state constituted the clinical picture in one and a typically toxic state, with bowel obstruction, the other. We wish particularly to record the roentgenologic features which we have not seen presented previously in cases with such extensive involvement. The disease is of interest at this time because of the recent literature which has been devoted to chronic non-specific enteritis and enterocolitis. Primary tuberculosis must be considered in all such cases occurring in early life when the involvement is extensive. The finding of tubercle bacilli in the stools repeatedly, in the absence of pulmonary tuberculosis, justifies a diagnosis of bowel tuberculosis.

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CHEMICAL SPECIFICITY IN GROWTH AND DEVELOPMENT*

By FREDERICK S. HAMMETT and STANLEY P. REIMANN, F.A.C.P.,
Philadelphia, Pennsylvania

THERE is steadily increasing recognition of the fact that fundamental cancer research does not necessarily mean the study of cancer. That cancer is just one phase of the growth problem is so self-evident that it admits of no argument. The problem, indeed, was placed on the doorsteps of biologists in this form many years ago by many of the great pathologists. In adopting this point of view, when the staff of the Lankenau Hospital Research Institute was organized some twelve years ago, we were promptly confronted with the confusion in which the word "growth" was floundering, a confusion recognized by but a meager few and compensated by them by using suitable adjectives to describe the kind of growth which they were discussing. We first attempted to clarify our thoughts in this matter, and then to interject some chemistry into them. This entrance of chemistry into the field is natural and surely requires no comment. We present in this paper, then, one particular aspect of chemistry as applied to growth, leaving the implications of this work to cancer research to the reader.

In the approach to any problem common sense suggests that extraneous matters be brushed aside. This is as necessary in the field of growth as anywhere else. For here as elsewhere there is, as stated, loose thinking and looser nomenclature.

The word growth is used to designate anything from elongation of a root to increase in area of a tissue culture; from metamorphosis of a tadpole to increase in weight of a rat. Yet anybody who thinks knows that each of these activities is expression of a distinct and individual set of processes.[1]

The time has come to get down to fundamentals, and it will be necessary first to consider the source of a reaction rather than the signs thereof.

Now there are four principal aspects of living things, viz., direction, substance, state of substance, and form. These are respectively subserved by the basic sciences of genetics, chemistry, physics, and anatomy. Genetics is primary because it determines the direction of succession and persistence. Chemistry is next in importance because without substance and its reactions there could be no expression of direction. Physics is third for through the state of substance the extent and rate of living are determined. And anatomy is basic because through structure function is expressed.

The substance of living things is composed of chemical atoms combined

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From the Lankenau Hospital Research Institute, Philadelphia, Pa.

into molecules. The activities of living are expressions of reactions between these molecules and their groups.

Growth is an activity of living. The substance of growth is therefore composed of molecules and groups, and growth is an expression of reactions between these chemical molecules and groups.

But what is growth? Is it simple increment or is it the expression of the sum total of processes used to bring an organism from its beginning to the functionally mature state?

To our mind growth is not single—it is multiple—the summated expression of integrated developmental and incremental processes, participants, and determinants.[2]

In this there are five chief sets of activities. There are the processes concerned in the preparation of the field for emergence of new structure. These are comprised in the developmental activity of **initiation**. There are the processes concerned in cell increase in number. These are comprised in the developmental activity of **proliferation**. There are the processes concerned in cell specialization or chemical individuality. These are comprised in the developmental activity of **differentiation**. There are the processes concerned in cell segregation or cell conjunction into functionable units. These are comprised in the developmental activity of **organization**. And there are the processes concerned in the incorporation of living substance into that already present. And these are comprised in the developmental activity of mass increment or **anabolism**.

Under these five may be encompassed all that concerns growth.

Each set of activities is obviously separate in function. But growth is not accomplished by their isolated expression. It is accomplished by the successive dominance of these activities in coterminous expression. That is to say, all work together but each predominates at some stage or another in the growth progression.

Each set of activities is also separate in expression as it is in function. Therefore each must have its own set of chemical participants, determinants, and reactions. Herein lies the chemical specificity of growth and development.

The chemical and functional specificities of vitamins, exocrine, and endocrine products are known, or are rapidly being uncovered. But these are not of present interest since they are not only late additions to developmental phylogeny, but also more concerned in adaptation of individuals than in developmental activities of general expression.

Our interest lies in finding the chemical nature of the participants, determinants, and reactions specific to those growth activities which are the common possession of all living things; those which are essential to the bringing of every living thing to completion. Attention is on the chemical specificities of **initiation, proliferation, differentiation,** and **organization.** It is not on the chemical specificity of root elongation in plants or bone growth in animals.

It is logical for this purpose then, to look to compounds which are components of living things in general, and to brush aside those which are limited in their occurrence to the particular.

In their application to cancer, it need be remembered only that cancer may be stated in all truth to be a deviation of growth possible in all living things, at least in all multicellular organisms.

These naturally-occurring tissue constituents of general distribution are nothing other than the amino acids and the nucleic acid components.

Knowledge of the specific function of any one of these ubiquitous compounds has hitherto been lacking. This is strange, for surely the specific functions of the substances of living are primary; and secondary are their general properties of acting as structural units, as energy producing combustibles, and as contributors to the reaction basis of living.

Because each of these compounds is present wherever substance is living, and because each has its own individual and specific chemical make-up and attributes, the hypothesis was set up by Hammett that each must have its own distinctly individual and specific part to play in some one or other of the several basic growth activities essential to the bringing of an organism from its beginning to its functionable maturity.

As stated, for the past twelve years investigations along this line have been pursued at The Lankenau Hospital Research Institute and its Marine Experimental Station.

The results have unquestionably validated the hypothesis and established it as an experimentally substantiated concept. There can now be no question but that each and every amino acid and nucleic acid component has its own characteristic influence on growth and that this can be traced to the specific character of the chemical configuration involved.

For these experiments it was necessary that an organism be used in which the various phases of growth and development could be separated, one from the other. Significant also would be conditions of metabolism as factors in growth and development. Thus when new tissue is being laid down by proliferation of cells, anabolism is in the ascendency. When differentiation is taking place within the protoplasm of the cells laid down by proliferation, chemical reconstitution is dominant; basic, more or less universal, compounds, groups and molecules are rearranged into specific and specialized kinds such as go into the make-up of epithelium, muscle, bone, nerve, or whatever tissue is being differentiated. When the completed animal is finished, neither anabolism nor catabolism is in the ascendency. There is maintenance metabolism whereby analytic and synthetic processes are nicely balanced in that dynamic equilibrium which is called "life." When regression sets in, catabolic processes are in the ascendency; larger and more specific molecules are broken down into simpler and more general molecules and groups.

As a beginning in this problem such an organism as the above necessities dictated was found in the marine hydroid *Obelia geniculata*. This is

a colonial-living animal attached by a stalk to a barnacle, shell, or convenient rock. From the main stalk grow side branches at the end of which completed organisms are developed. Two types can be recognized, one, the gonophore, producing medusae, and the other, the vegetative form, or the hydroid itself. On the stalk, or one of its branches, there appears a bud which increases in size by proliferation, anabolism being in the ascendency. The bud continues proliferation and a cone-shaped end is developed. Inside of this cone-shaped structure differentiation occurs and then organization of the differentiated structure until the complete animal with its tentacles is the final result. After a time regression sets in; the tentacles slowly disappear and the protoplasm within the cup-shaped body undergoes disintegration, finally leaving an empty cup as the end result of its life cycle. During the differentiating stage there is chemical reconstitution to produce the complete organism. During its span as complete animal, metabolism is of the maintenance variety. During regression catabolic processes are in the ascendency. During the course of these processes protoplasmic streaming occurs from the main stem predominantly outward into the bud. That is, during this period fresh building blocks are carried to the organism for its use in chemical addition and reconstitution. During the mature stage the stream is backward and forward; during the period of regression the stream is predominantly inward toward the main stalk. For convenience the stages of growth and development can be divided into one-fourth developed, one-half, three-fourths, complete, and senile.

Recording of the results of the experiments was dynamic. Records were made of the condition of organisms at the beginning of an experiment. They were then exposed to the effects of a number of chemical compounds for a given length of time. At subsequent examinations the stages reached by the various organisms were again recorded. As an example, if, in a given group 25 were in the half stage, and 25 in the three-fourths, record was made of the progress from the proliferation to the differentiation stage; and from the state of differentiation to that of organization to the complete functionable animal. Thus the effects of any given chemical compound on initiation or proliferation or differentiation or organization were recorded. Following is a list of compounds which have been tested, and a statement of results. For further details reference is made to original publications.

Glycine accelerates regeneration.

Alanine has no apparent effect on the growth of the animal other than that which can be attributed to its specific dynamic action.

Phenylalanine may, as a potential source of tyrosine, forward differentiation.

d-Glutamic acid hastens differentiation and organization.

Tryptophane retards catabolism and thus may indirectly stimulate general growth.

Histidine may act similarly through its sustaining effect on metabolic expenditure.

Uracil favors recurrent growth and retards differentiation, regeneration and metaplasia.

d-Arginine has an effect similar to that of Uracil, which suggests the latter as a natural precursor of the former.

d-Ribose has no specific effect on any of the developmental growth activities.

Allantoin might favor growth in general but it has no specific influence on increase in cell number.

dl-Methionine stimulates proliferation. Results are consistent with the assumption that methionine may be converted to cystine in the living organism.

l-Aspartic acid is specific for differentiation.

d-Lysine is essential to mass increment by participating in some intermediary process.

Thymine is significant in proliferation and differentiation.

Cytosine helps differentiation.

l-Hydroxyproline accelerates proliferation and differentiation.

l-Proline forwards differentiation and retards proliferation.

Adenine enhances organization and retards initiation.

Xanthine forwards regeneration.

Guanine forwards initiation and organization.

From these results there emerge a number of generalizations. But one will be mentioned.

The compounds which influence differentiation are d-glutamic acid, l-aspartic acid, l-proline, l-hydroxyproline, tyrosine, cytosine and thymine. These in common may yield a single type of chemical grouping, viz., the pyrrolidone configuration. Perhaps it is this simple chemical group which is found so freely and frequently in intermediate metabolism that is the chemical key for the unlocking of that chemical specialization of cells which is called differentiation.

The experiments to be done in relation to cancer are obvious. Anatomically, cancer cells do not differentiate normally and do not organize at all. Is it because the cells cannot by reason of a changed internal chemical make-up, or is it because the environment does not furnish the requisite building blocks? Offering to cancer cells, compounds with the pyrrolidone configuration actually or potentially present should help decide this long-asked question.

Summary

Fundamental cancer research does not necessarily mean that cancer itself is studied. Cancer is but one phase of the growth problem; therefore studies of growth in general have some bearing on cancer. The word "growth" is ambiguous and so should be modified by adjectives or phrases such as growth in size, growth in number, differential growth, developmental growth, etc., when discussed.

The entrance of chemistry into the growth problem is natural. The particular discussion of the paper, of which this is an abstract, is concerned with this question. Inside of cells are numbers of chemical molecules, groups and atoms. What do they do inside of cells in relation to growth and development? The amino acids and certain nuclear compounds have been studied and it is found that each one thus far tested has its own particular part to play in growth and development. There is then chemical specificity for the various phases of growth. The effect of these compounds

will be enumerated. A few problems will be set up from these results in direct relation to cancer.

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CASE REPORTS

HYPERACTIVE CAROTID SINUS MECHANISM IN AURICULAR FLUTTER; A CASE REPORT*

By N. Hiatt and L. Adams, *Chicago, Illinois*

The combination of auricular flutter and a carotid sinus sufficiently hyperactive to lead to syncopal attacks and convulsions has not hitherto been reported. Such a case was recently seen at the Michael Reese Hospital and because of its rarity is presented in this communication.

Case Report

The patient, a 66 year old white streetcar motorman, first entered Michael Reese Hospital in July 1936, because of hunger, thirst and polyuria, which had been gradually increasing during the preceding three years. One week before entrance to the hospital, the patient had fainted while driving his streetcar. The doctor consulted at this time discovered a four plus glycosuria and a blood sugar of 206 mg. per cent, and sent him into the hospital in order to control the diabetes.

The family history was not contributory. The fainting spell of a week before admission was identical with several he had had in the six months preceding. While maneuvering his streetcar from the barn in the morning, he would suddenly faint. After lying down for several minutes, he would arise feeling perfectly well and continue his day's work without interruption. In addition, for the past two or three years he had noticed that extreme dizziness would follow any attempt to look upward abruptly. In fact, this condition had become so extreme that the patient could not mount more than one rung of a ladder without falling. Finally a history of increasing exertional dyspnea for the past 15 years was elicited. At the time of admission a two-block walk made the patient short of breath. There was no associated pain, palpitation or other evidence of diminished cardiac reserve.

The pertinent physical findings discovered on this admission were: mouth edentulous; two small areas of leukoplakia on the right lower alveolar ridge; considerable angiosclerosis of the retinal vessels; the apex of the heart could be palpated just beyond the nipple line and the heart tones were distant; the contour of the chest was emphysematous and the peripheral vessels were sclerotic.

The blood pressure on admission was 156 mm. of mercury systolic and 70 diastolic. Wassermann and Kahn tests were negative, blood non-protein nitrogen was 32 mg. per cent and the sugar 220 mg. per cent. Except for four plus sugar, the urine was negative.

During this stay in the hospital, the temperature was always normal and the pulse always regular, varying between 60 and 80. The diabetes was rapidly controlled by means of diet and insulin, and the patient left the hospital in 10 days with no glycosuria and a blood sugar of 90 mg. per cent. After his discharge from the

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hospital, the patient was free from diabetic symptoms although he was prone to be careless with his diet and to take insulin irregularly.

A year and a half later, in January 1938, the patient returned to Mandel Clinic complaining of a painless, intermittent hematuria of a week's duration. He was put on a diabetic diet with small amounts of insulin and sent into the hospital. The fainting spells which accompanied his attempts to maneuver his streetcar from the barn in the morning had become so frequent that he had been retired from his job on a pension. Since stopping work, he had had no more fainting spells, although he still occasionally became dizzy when he looked up abruptly.

In addition to the previously noted positive physical findings, those on his second admission were: blood and blood clots in the second glass of urine, evidence of some weight loss and a moderately enlarged, non-tender, nodular prostate.

The blood pressure was 155 systolic and 80 diastolic, and the blood count and blood chemistry (including the blood sugar) were perfectly normal throughout the hospital stay.

Soon after admission the patient was cystoscoped and a tumor mass infiltrating the vertex and posterior wall of the bladder was discovered, biopsied and thoroughly fulgurated. The biopsy report was squamous carcinoma of the bladder. In 10 days the patient left the hospital with a clear urine.

During this stay in the hospital, the pulse was always between 70 and 90, and regular.

In March 1938, some six weeks after leaving the hospital for the second time, the patient returned to the Mandel Clinic with pain in his right lower jaw. Beneath his denture, on the right alveolar ridge, was discovered a raised, hard, granular area extending from the second bicuspid to the retromolar triangle. No associated lymph nodes were found, nor did roentgen-ray reveal any invasion of the mandible or metastases to the chest. The biopsy disclosed no definite evidence of carcinoma. The lesion was treated with radium and, after six weeks of treatment, disappeared.

In September of 1938, the patient was cystoscoped again and a small recurrent papillary tumor discovered at the trigone. Before the patient could be sent into the hospital, however, it was noted that he had a pulse rate of 152, which was perfectly regular. Consequently the patient was sent to the cardiac out-patient clinic before being admitted to the hospital. Here, in addition to the old history of exertional dyspnea, mild orthopnea and nocturnal cough for the past few months were reported. The only additional positive physical findings at this time were a very light pitting edema of the lower extremities and a slowing of the pulse on carotid sinus pressure. The blood pressure was 150 systolic and 90 diastolic, the pulse 150 and regular. A roentgen-ray plate showed heart enlargement (13.7/26.7 cm.), chiefly of the left ventricle. An electrocardiogram showed a left ventricular preponderance and an auricular flutter, with an auricular rate of 300, a ventricular rate of 150, and two to one conduction.

The patient reëntered the hospital on the genito-urinary service in October 1938, for refulguration of his bladder tumor. The physical findings were essentially the same as those of the past two and a half years, except that on occasion a soft systolic blow was heard at the apex of the heart, and the liver was felt two fingers-breadth below the costal margin.

The urine contained many red blood cells but was otherwise negative. The blood count and blood chemistry (sugar and non-protein nitrogen) were within normal limits during his entire hospital stay. By means of diet and a small amount of protamine insulin (U 10) the patient's urine was kept sugar-free, and blood sugar was held around 100 mg. per cent. The blood pressure on admission was 140 systolic and 100 diastolic and thereafter varied between a maximum of 150 systolic and 100 diastolic postoperatively to a minimum of 140 systolic and 80 diastolic on discharge. The pulse on admission was 140 and regular. During the hospital stay, it was always regular and

generally ranged between 120 and 160. On several occasions, however, it fell to 80 or 90, although never for more than 10 to 20 minutes.

Soon after admission the patient's bladder tumor was again thoroughly fulgurated. The postoperative course was entirely uneventful, and after several days, when he was again completely comfortable, the patient was transferred to the medical service of Dr. L. Bloch because of the persistent tachycardia. It was now discovered that eyeball pressure slowed the pulse rate; also that momentary compression of the right carotid sinus when the patient was sitting up caused the ventricles to stop instantly and the patient to become unconscious almost immediately and have a convulsion soon after. Later the patient identified this episode with the fainting spells which had led to his retirement a year and a half before. Irritation of the carotid sinus by metastatic malignancy was suspected, in view of the fact that the patient had been treated only six months previously for a lesion of the mouth that was possibly a carcinoma. A careful search, however, revealed no demonstrable nodes in the neck, nor any evident lesions of the larynx, pharynx or pyriform sinuses.

Two weeks postoperatively the patient was discharged with a normal urine, and with his diabetes under control. No attempt was made to convert the flutter at this time, nor to denervate the carotid sinuses, because the patient became uncoöperative.

Discussion

During his stay in the hospital, several procedures were carried out which helped to illuminate the mechanism of his fainting attacks and convulsions. The patient was not coöperative at any time, because he was convinced that the tests were affecting his heart. He did not regard the unconsciousness incident to the pressure on the carotid sinus as unpleasant, but after the first few tests, refused to stand or sit up during carotid sinus stimulation. Consequently all of the electrocardiographic studies were done in the supine position.

A typical convulsive seizure, while the patient was standing or sitting, could be precipitated by pressing on the right carotid sinus for about a second. The sequence of events was uniform. Almost simultaneously with the application of the pressure the pulse disappeared, the patient began to sweat slightly, became extremely pale and lost consciousness. Generalized convulsive tremors appeared after about 15 seconds, accompanied by a right deviation of his head, exophthalmus and a coarse nystagmus to the right. At this time, the pulse could always be felt, beating slowly and irregularly. After about 20 seconds of convulsions, the patient regained consciousness, his face became flushed, the convulsive movements rapidly subsided, and the regular rapid pulse returned. The entire episode lasted about one minute. Subjectively, when the right carotid sinus was pressed, the patient felt faint, the sensation being identical with that experience during the fainting spells that he had had for the past two and a half years. Pressure on the left sinus caused an almost identical effect, including the turning of the head and nystagmus to the right.

With the patient supine, his head supported by one pillow, asystole and unconsciousness (which seemed to parallel each other) could readily be elicited by pressure on either sinus. Convulsive movements, however, occurred inconstantly, and then only with pressure of five seconds or more. Pressure over both sinuses for from one to three seconds while the patient was supine was as effective as pressure over either one when he was erect.

The studies in which the electrocardiogram was recorded were all done when the patient was supine. Analysis of the records showed an auricular flutter, with an auricular rate of 300 and a ventricular rate of 150.

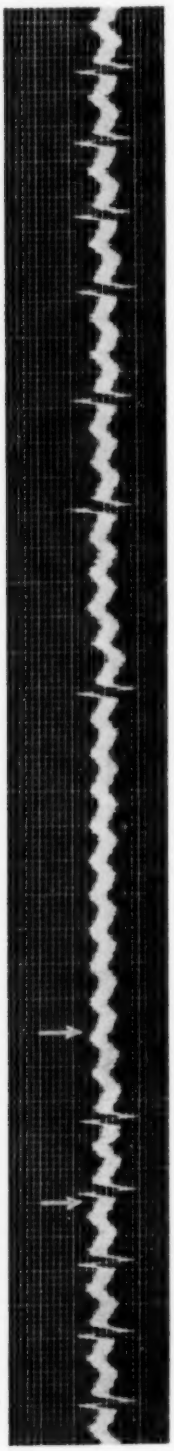

FIG. 1. Effect of compression of the right carotid sinus for one second (Lead II). Arrows mark out time of compression. Note short period of ventricular asystole.

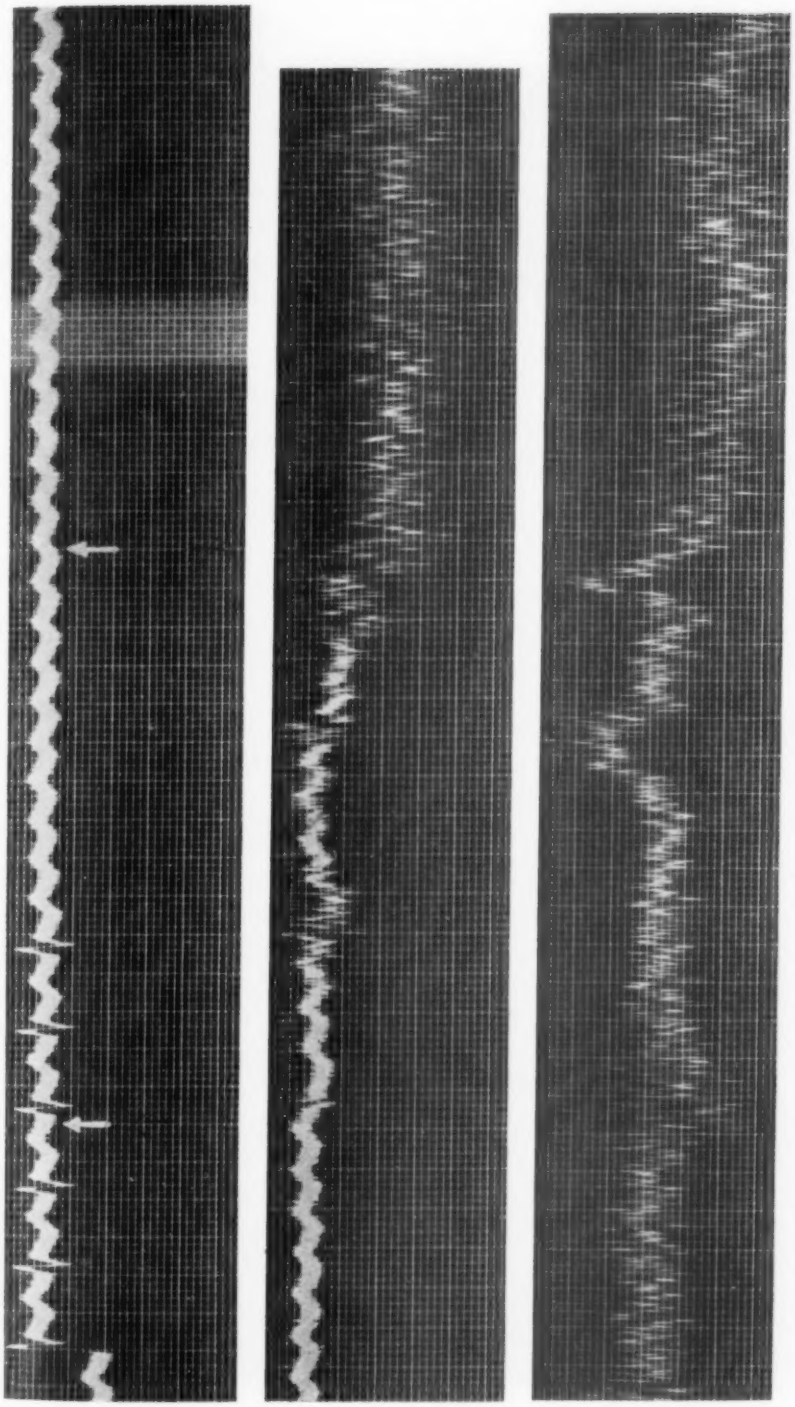

FIG. 2. Effect of compression of both carotid sinuses for three seconds (Lead II). Arrows mark out time of compression (a continuous record). Note long period of asystole and evidence of convulsions, the latter starting after the former and outlasting it. Also note the second period of convulsions without ventricular asystole or other evidence of circulatory disturbance.

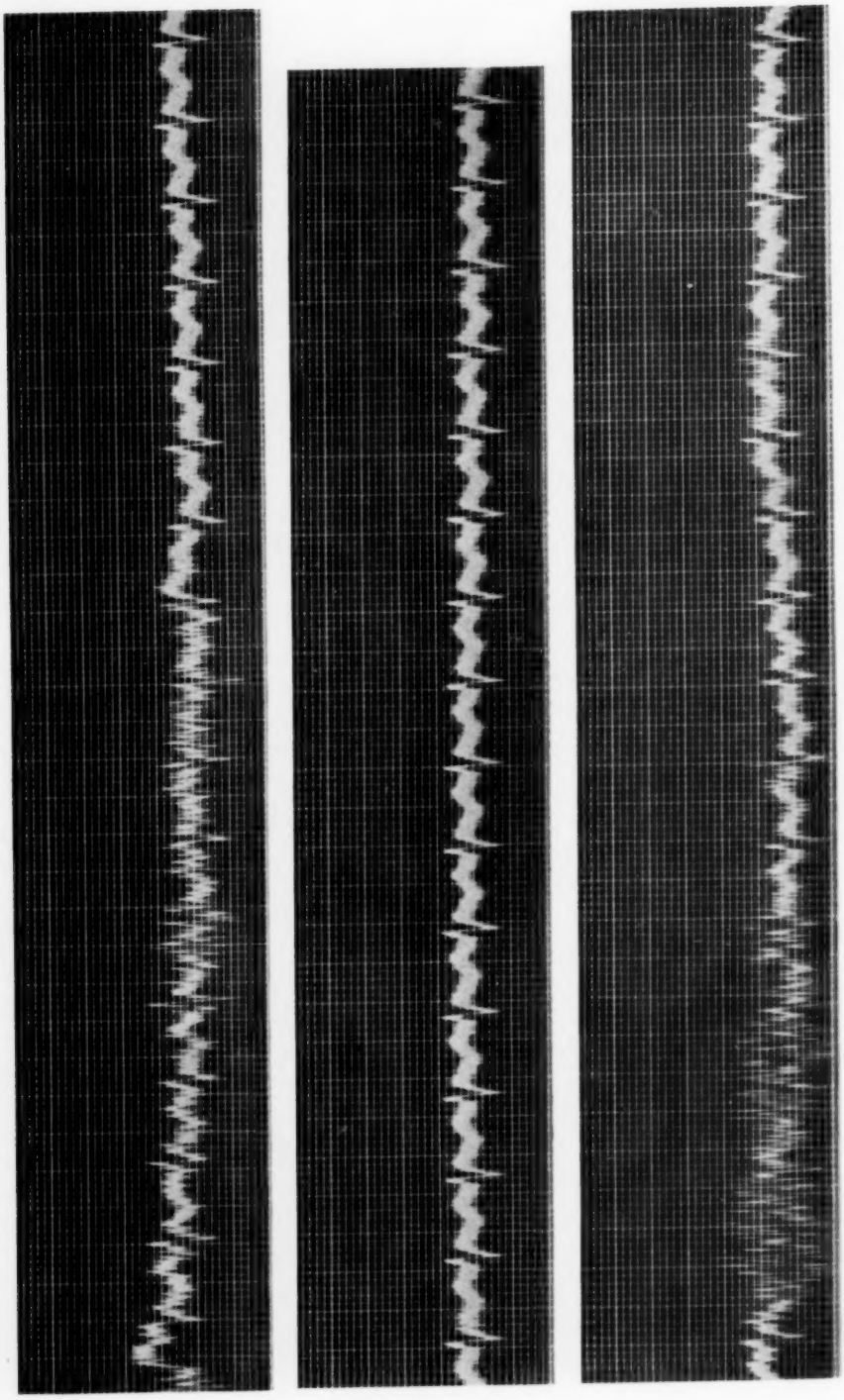

FIG. 2. (*Continued.*)

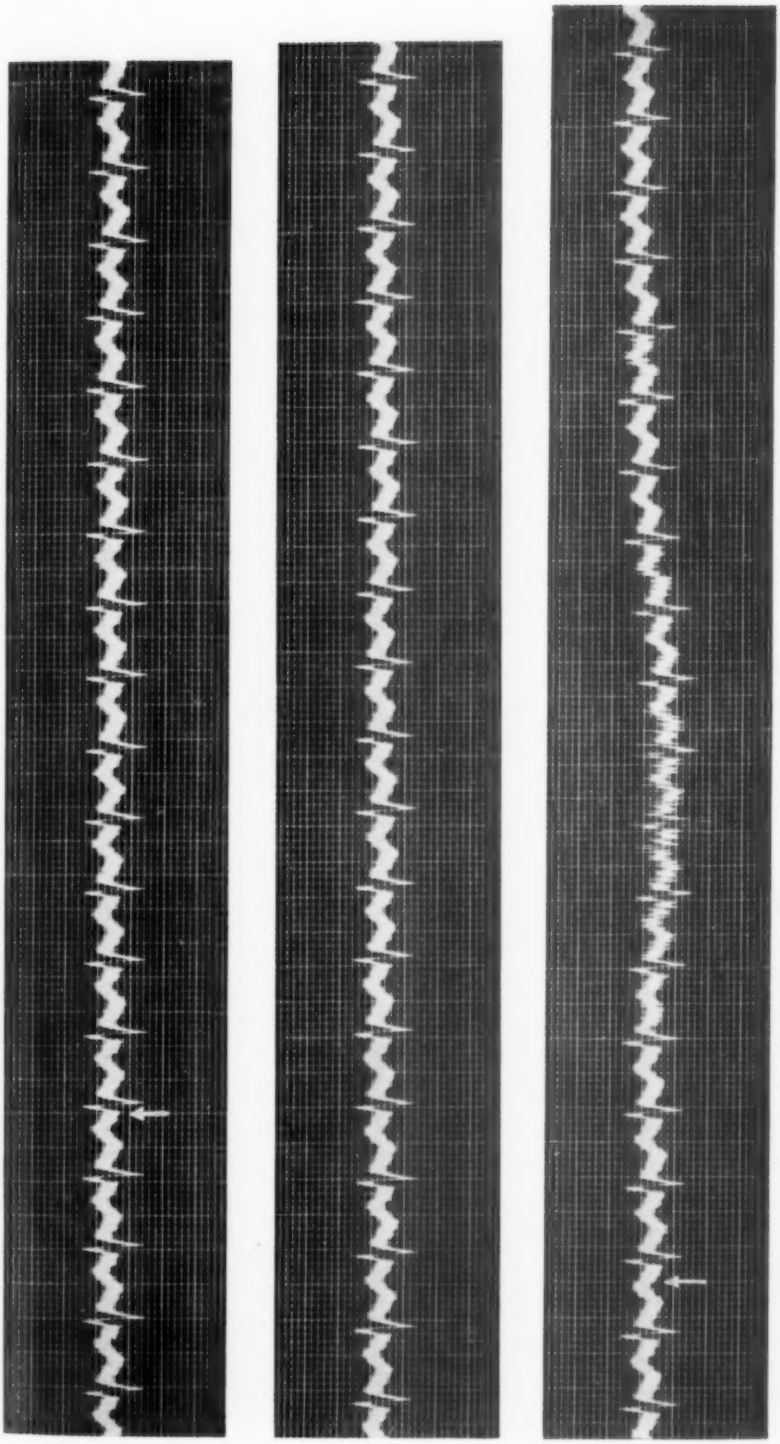

FIG. 3. Effect of compression of the left carotid sinus for 15 seconds after the patient was given 1/15 grain of atropine (Lead II). Arrows mark out time of compression (continuous record). Note convulsion following compression unassociated with any change in ventricular rate or other evidence of circulatory disturbance.

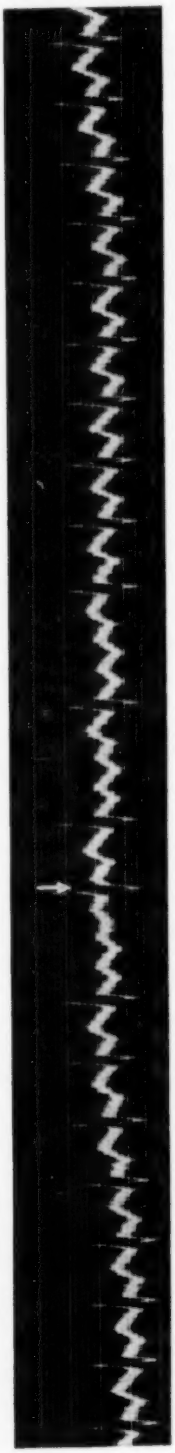

FIG. 4. Slowing of the ventricular rate following the compression of both eyeballs for five seconds (Lead II). Arrow represents when compression was stopped.

Compression of the right carotid sinus for one second caused, after a lag of two or three beats, a complete asystole lasting 2.4 seconds (figure 1). The onset of the asystole was abrupt, and the block was immediately complete. The offset, however, was gradual and extended over 4.6 seconds, during which time three ventricular systoles occurred, with a progressively improving A–V conduction. There was no change in the flutter rate during the entire period of observation. On recovery from the effects of the carotid sinus pressure, the ventricle resumed the pre-compression rate of 150. The same abrupt and rapid onset of asystole of the ventricles and the relatively gradual offset occurred with either gradual or abrupt compression of the right carotid sinus. Three-second compression gave rise to periods of asystole and relatively slow beating about twice as long as those obtained with one-second compression. Compression of the left carotid sinus gave results identical with those following compression of the right, except that the periods of asystole and slow beating were about one second shorter. In every case, on application of pressure the patient felt faint and lost consciousness almost simultaneously with the onset of asystole; this unconsciousness lasted during the absolute asystole, and disappeared during the period of slow beating. In the supine position, there was no well-defined pallor or flushing such as was noticed when the patient was erect.

Simultaneous compression of both sinuses in the supine position for three seconds gave results similar to those observed after compression of the right sinus alone in the erect position. Convulsions began after seven seconds of asystole, and these were identical with those previously described (figure 2, second, third and fourth strips). However, about 10 seconds after the end of the convulsion, when the pulse had returned to its pre-compression rate of 150, the patient had another convulsion less extensive and shorter than the first, but otherwise very similar in external appearance (figure 2, sixth strip). No blood pressure readings were made during these convulsions.

The patient was given atropine, gr. 1/15 hypodermically—a dose certain to abolish the vagus effects. There was no change in the auricular or ventricular rate after the patient was atropinized. Half an hour after the atropine was given each carotid sinus, and then both together, were compressed for three then five seconds, with no effect on the auricular or ventricular rates, no unconsciousness or sense of faintness. However, when either carotid sinus was compressed for 15 seconds, the patient had a small and short, but quite typical convulsion, during which time he again felt as though he were fainting (figure 3, third strip). This occurred without change in the pulse; no blood pressure readings were obtained. He could not be prevailed upon to sit up and permit us to repeat this procedure.

In short, it appears that in this patient the abolition of the ability of carotid sinus stimulation to cause asystole of the heart did not entirely abolish its ability to cause convulsions. This, and the fact that after bilateral sinus compression there occurred a convulsion without coincident asystole (figure 2, sixth strip), suggest that the mechanism causing convulsions and that causing cardiac asystole are not identical.

The use of atropine in doses adequate to abolish any cholinergic stimulation following carotid sinus compression[1, 2] served several purposes. It demonstrated that the asystole of the heart was due to an action of the vagus on the A–V conduction system. In addition, it showed that the flutter was probably

not a transient one due to tonic carotid sinus activity; carotid sinus pressure may give rise to transient runs of auricular flutter.[3] The use of atropine also indicated that the convulsions were not entirely related to the asystole, but could occur without it, either, as thought by some, as a result of reflex constriction of the cephalic vessels [4, 5, 6, 7] or of some other obscure neurogenic process. A vasomotor dilatation with drop in blood pressure and resultant cerebral anemia was not absolutely ruled out, but the absence of any change in the pulse makes this unlikely. Finally, the use of a large dose of atropine showed that this drug itself is probably not sufficient to bring about 1 to 1 conduction in auricular flutter, although it may increase the ventricular rate when the conduction ratio is low [8] just as it prevents the lower conduction ratios during carotid sinus stimulation.

The effect of carotid sinus pressure on the heart with fluttering auricles is not uniform. The slowing of the ventricular rate is not a constant occurrence even in cases where the heart can be slowed by ocular pressure.[9, 10] This failure to elicit slowing may be due to an inability to locate the carotid sinus, whose position in the neck is not constant.[11] It is generally agreed that carotid sinus stimulation slows the ventricular rate in auricular flutter by increasing the A–V conduction time up to complete block.[9]

There is somewhat more variation of opinion concerning the effect of vagus stimulation on the fluttering auricles. Clinically, most observers using ocular or carotid sinus pressure report that there is no vagus effect on the auricles in auricular flutter.[10, 12, 13, 14, 15] Others, however, using similar methods, as well as direct stimulation of the vagus nerve in the dog, have reported either an increase in the flutter rate [16, 17] or a change in the configuration of the auricular waves.[18] In the case here presented, where an extremely active and sensitive carotid sinus mechanism was present, we felt that any vagus effect on the auricles, if it existed, would be exaggerated. However, no change was observed either on the rate of the auricular flutter or on the configuration of its waves.

It is interesting to note in this case the almost equal effectiveness of the two carotid sinuses in producing A–V block, and their equal ineffectiveness on the auricles. It is probable that the auricular flutter and hyperactive carotid sinus are coincidental. It is true that in persons with generalized arteriosclerosis and coronary sclerosis the carotid sinus reflex tends to be more active than in other age groups,[19] and that this is the group in which one frequently sees auricular flutter, often with no other evidence of heart disease.[20]

The oculo-cardiac reflex was less effective in our case than the carotid sinus reflex; nor did it appear to be enhanced by the presence of a hyperactive carotid sinus reflex (figure 4). There was definite evidence that the activity of the carotid sinus of our patient was abnormal. In the first place, very brief sinus compression quickly led to asystole of considerable duration, as well as to convulsions. Second, the sequence of events in this case was very similar to that following carotid sinus pressure in patients having known hyperactive carotid sinuses and sinus rhythm.[21, 22] While it is possible that the earlier fainting spells before the last admission represent an auricular flutter with periods of 1 to 1 conduction,[23] or paroxysms of auricular flutter, this is unlikely in view of the mechanism found during the patient's last hospital stay.

Summary

We have presented a patient with a hyperactive carotid sinus and auricular flutter. We have been able to show that the flutter was not due to a tonic activity of the vagus, and that even in the presence of a hyperactive carotid sinus mechanism vagus stimulation does not affect auricles which are fluttering. Finally, in this case we were able to demonstrate that the patient's convulsions, which appeared when either carotid sinus was stimulated, were not entirely due to the asystole which the stimulation brought about.

We are indebted to Dr. L. Block for permission to report this case, and to Dr. L. N. Katz for his suggestions in analyzing the mechanism and in preparing the report.

Note: While this paper was in press, the patient came in for fulguration of his bladder tumor; soon thereafter he developed frequent fainting spells and convulsions. Electrocardiograms revealed these to be due to paroxysmal ventricular flutter and fibrillation; one of these was irreversible and the patient died. No autopsy was obtained.

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A CASE OF ACUTE IDIOPATHIC HEMATOPORPHYRIA WITH ACUTE ASCENDING PARALYSIS *

By Harold W. Palmer, M.D., F.A.C.P., *Wichita, Kansas*

In 1911, in his original monograph, Günther [1] described a rare constitutional disturbance which he called hematoporphyria, the essential symptom of which was the finding of large quantities of hematoporphyrin in the urine. He later made the statement, confirmed by Hoppe-Seyler, that hematoporphyrin was not the pigment found in the urine in this disease, but that the pigments actually were copraporphyrin and uroporphyrin, related substances. However, through general acceptance by Garrod and others, the pigment is still referred to as hematoporphyrin and the disease state as hematoporphyria. In 1925 Günther [1] attempted to classify the hematoporphyria into three separate groups, namely, (1) congenital hematoporphyria, (2) acute idiopathic hematoporphyria, and (3) acute toxic hematoporphyria. Of the first group, the congenital, he was able to collect 18 reported cases, to which Mason and Farnham,[2] reviewing the literature in 1931, were able to add six cases, bringing the total to 24. The characteristics of this group are that large quantities of hematoporphyrin are found in the urine often associated with other unidentified pigments together with a bullous eruption on the exposed surfaces of the skin following exposure to sunlight. These cases are found in children and young individuals and the condition may be present from birth. The disease is often familial and in recent reports, at least in isolated instances, seems to follow Mendelian lines.[3] The skin lesions may be quite deep seated with intensive scar formation and mutilation of parts affected. Often cases showing so-called pink teeth are noted, the teeth being stained brown or pink. Enlargement of the spleen is often an associated finding, as is also a moderately severe secondary anemia.

The second group defined by Günther [1] contains the acute idiopathic type of case. In this group he referred to 18 proved cases; but Mason, Courville and Ziskind,[4] reviewing the literature in 1933, were able to bring the total to 46 authenticated cases.

Of the third group, the acute toxic type, Mason, Courville and Ziskind [4] were able in 1933 to find 100 cases. Of these 86 had used sulphonal and 11 had used trional. Lead, veronal and other barbiturates have been reported as etiological

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From the departments of Medicine and Pathology, Wichita Hospital, Wichita, Kansas.
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agents. Clinically the two groups, the acute idiopathic and the acute toxic, are identical except that in the former the etiological agent is unknown whereas in the latter a history of the excessive use of sulphonal, trional or other barbiturate is found. Lead has also been reported as a toxic agent in this group.

Because acute idiopathic hematoporphyria is relatively a rare disease it was thought that a clinical case report with autopsy findings would be of interest. Mason, Courville and Ziskind [4] state that they found in 1933 that only 12 of the 46 reported clinical cases had come to autopsy.

Case Report

Mrs. L. H., white female, aged 26, was admitted to the hospital June 28, 1938, with the history that about 10 days previously her acute illness had begun with pain in the back. The pain was described as severe, requiring morphine for relief. Shortly after this she complained of burning pain in the bottom of her feet, this

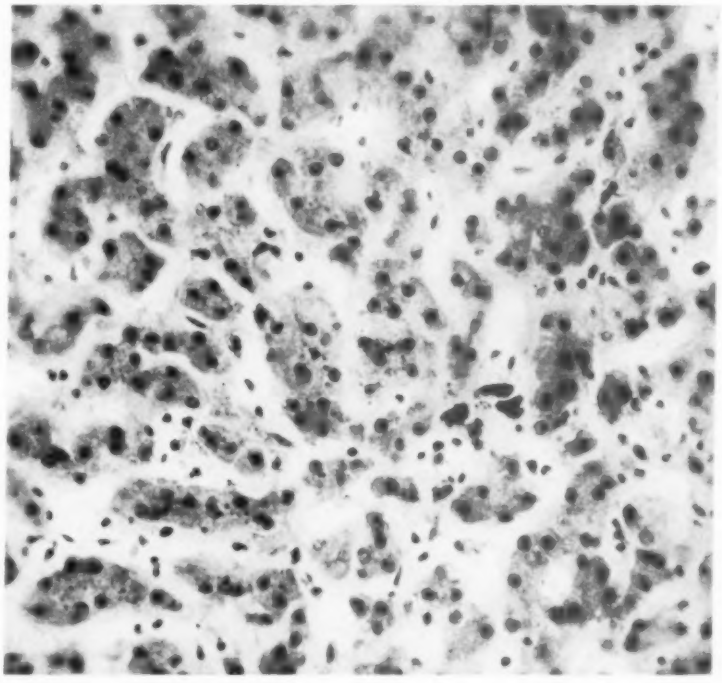

Fig. 1. Section of liver showing marked degenerative changes of the cords with stippling of the Küpffer cells and larger amorphous pigment deposits. Hematoxylin and eosin stain. Magnification × 280.

being followed by complete loss of use of the legs accompanied by intense pain in all the leg muscles. A few days later the paralysis had progressed to the arms, accompanied by intense pain in all the arm muscles. The generalized paralysis was accompanied by spasmodic twitching of all the involved skeletal muscles. There was no history of the use of sulfonal, veronal, trional or exposure to lead.

Her past history showed that she had always been nervous and underweight. At 16 years of age she had had an acute illness with abdominal pain and vomiting which was thought to have been a liver disturbance, but no jaundice was noted at

that time. The color of the urine at that time was not observed. At 20 years of age she had a Bell's palsy, the duration of which was about six weeks. At the age of 22 she had married and had had her first pregnancy which was uneventful. The hospital record shows the urine to have been normal in color at that time. During the course of her second pregnancy at 23 she frequently noted that the urine was dark brown in color. She had nausea and vomiting for the first three months of

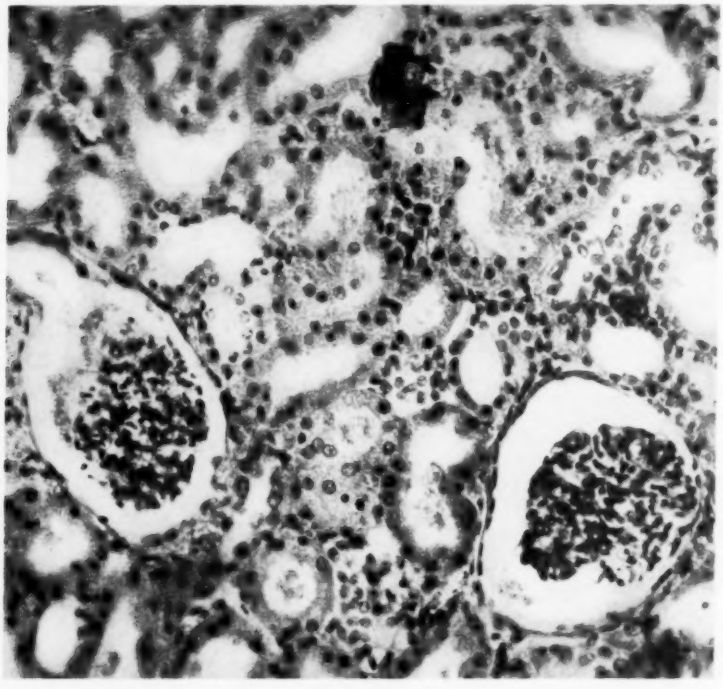

FIG. 2. Section of kidney showing marked degenerative changes in tubular epithelium and glomeruli with deposits of pigment in the epithelium of the tubules and in the glomeruli. Hematoxylin and eosin stain. Magnification × 280.

this pregnancy but again delivered at term normally. The hospital record again shows the urine normal in color at the time of this delivery. About three months previous to the present admission she had had a miscarriage, when she was about three months' pregnant, from which she made an uneventful recovery without surgical interference.

On examination she was very thin, emaciated and dark skinned, weighing not more than 90 pounds. No jaundice was present. There was complete paralysis of all the muscles of the arms and legs with marked atrophy of all groups. A bilateral wrist and ankle drop was noted. There was marked tenderness to slight pressure over all the skeletal muscles, but cutaneous sensibility to pain, heat and cold stimulation was normal and she readily identified common objects placed between the fingertips. All deep tendon reflexes were absent except that of the right tendon Achilles which was present and active. The Babinski sign was negative on both sides. Respiration was deep and labored although no actual air hunger or cyanosis was apparent. Difficulty in swallowing was noted even with water, and choking resulted when liquid was taken rapidly. Articulation was difficult and the speech might be described as being explosive in character.

Examination of the external ocular muscles was negative, but there was a slight ptosis of the left upper lid. The pupils were large but reacted to light and accommodation. The eye grounds were normal. The tongue protruded in the midline with slight tremor. The ribs were plainly visible through the chest wall because of the lack of subcutaneous fat. The heart and lungs were entirely normal. The pulse was constantly rapid with an average rate of about 120 per minute. The blood

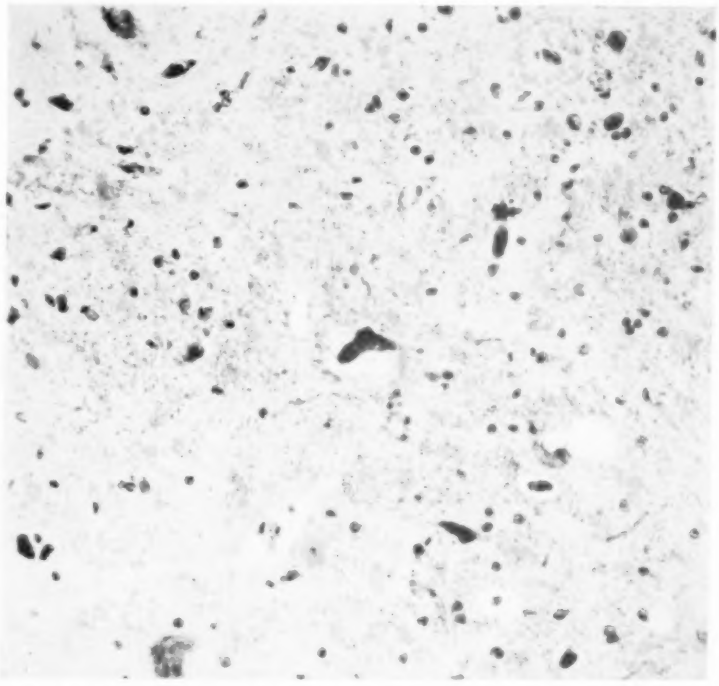

FIG. 3. Section through anterior horn of the spinal cord showing marked pyknosis of the anterior horn cells with diffuse deposits of pigment. Hematoxylin and eosin stain. Magnification × 280.

pressure was 106 systolic and 70 diastolic. The abdomen was sunken, and the iliac crests prominent. The spleen and liver were not palpable and no masses were felt. Examination and inspection of the vagina, cervix and pelvic contents was negative.

Laboratory Examination: The red blood cell count was 3,960,000 and hemoglobin 80 per cent (Newcomer). The white blood cell count was 9,500 and the differential showed 63 per cent polymorphonuclear cells, 15 per cent band forms, 15 per cent lymphocytes, 5 per cent metamyelocytes, 1 per cent basophiles, 1 per cent eosinophiles. The color of the urine varied from a reddish brown to brownish black. The specific gravity ran from 1.013 to 1.022. All examinations for albumin, sugar, bile, acetone and diacetic acid were negative. Urobilin was found in large quantities. The spectroscopic examination by Garrod's method showed the characteristic absorption bands for hematoporphyrin on two different occasions. Examinations for blood, blood pigment and iron were negative. The spinal fluid pressure was low, the fluid was clear and contained no cells and no globulin. The Lange test was negative. The fragility test on the red cells was normal, showing beginning hemolysis at 0.42 per cent NaCl concentration. The blood serologic and chemical tests were as follows:

Wassermann on both blood and spinal fluid was negative.
Blood sugar: 129 mg. per 100 c.c. of blood.
Blood calcium: 11 mg. per 100 c.c. of blood.
Blood cholesterol: 144 mg. per 100 c.c. of blood.
Blood urea: 72 mg. per 100 c.c. of blood.
Blood creatinine: 1.3 mg. per 100 c.c. of blood.

No basophilic stippling (lead) was noted and no arsenic could be demonstrated in the urine.

Course: The temperature at no time was over 99.2° F. and for the most part was below 98.6° F. The pulse remained rapid, ranging from 110 to 130 per minute. Breathing gradually became less labored and on discharge from the hospital August 5, 1938, 38 days after admission, swallowing of liquids and soft foods was normal. Constipation was a prominent symptom and only on one or two occasions was lack of sphincter control for urine and feces recorded. At the time of discharge from the hospital the peripheral sensory examination was still normal. Some improvement in the motor paralysis was noted but the degree of recovery was not marked. Mentality was clear until a few hours before death and at no time during the course of the disease were hallucinations or delusions noted. Pigmentation of the skin, especially over the hands, was quite marked for a period of two weeks previous to death. She died at her home on August 22, 1938, about two months after the onset of her acute illness.

Therapy: Morphine was used for the relief of pain, salicylates proving of no value. During the stage of partial bulbar paralysis nutrient proctoclysis was resorted to. Vitamin B concentrate was administered with the hope that it would have a beneficial effect on the neurological lesions. No calcium was given in this case, although beneficial results have been reported from its use intravenously.[3]

Autopsy: The autopsy was performed about six hours after death. The body was that of a very emaciated young white female. The skin was almost bronze in color, the pigmentation being most marked on the hands. Numerous small cutaneous blebs were noted over the abdomen. There was no evidence of jaundice present. The pericardium contained about 50 c.c. of thin clear yellow fluid, and the surface of the heart was smooth. There was no hypertrophy of this organ and the valves were all normal. The lungs contained air except in the dependent portions where some bloody fluid was present. There were no pleural adhesions and no areas of gross consolidation were noted. The liver was slightly enlarged and had a deep reddish brown color. The surface was smooth and the cut section showed the same deep pigmentation as the surface. The gall-bladder contained one small soft cholesterin stone. The pancreas showed no abnormalities. The spleen was about twice average size and the cut surface was deep red in color. The pulp scraped easily. The bladder was opened and contained about 50 c.c. of a dark red urine. The wall of the bladder was slightly thickened. There were no gross abnormalities in any of the pelvic organs. The gastrointestinal tract was negative except for a large fecal mass in the rectum. The kidneys were normal in size and consistency but also showed the reddish brown color both on the surface and on cut section. The adrenals showed no unusual changes. On exposure of the brain, the meninges and convolutions showed no gross pathological alteration. The ventricles were not dilated. Blocks were taken from the internal nuclei on either side and in the region of the third ventricle. Also blocks were taken from the pons, cerebellum and various portions of the brain stem. The spinal cord was exposed and blocks were taken at frequent intervals along its entire length. Blocks were taken from the left popliteal nerve and from the left brachial plexus.

Histopathology: Heart: All sections showed poor staining of the cross striations of the fibers. In some areas interstitial round cell infiltration was noted while in

others hemorrhage was present in the interstitial spaces. Fatty degeneration of the muscle fibers was quite evident in some of the sections.

Liver: A high degree of diffuse cloudy swelling was present going on to almost complete atrophy of the cords in some areas. The Küpffer cells showed extensive stippling with pigment which on differential staining with Prussian blue was found to be iron containing. Larger amorphous masses of iron free pigment as differ-

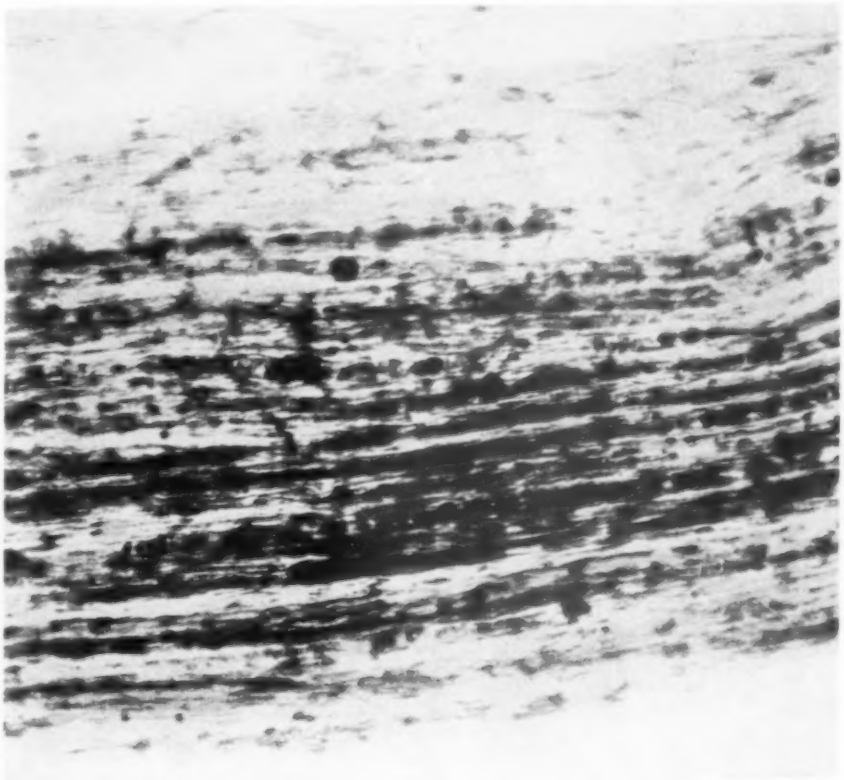

FIG. 4. Longitudinal section popliteal nerve showing moth-eaten appearance of myelin sheaths. Speilmeyer stain. Magnification × 280.

entiated by Prussian blue staining were also found in the Küpffer cells in all the sections. There was a perivascular round cell infiltration noted in some areas and in others groups of round cells were seen in the interstitial tissue.

Spleen: Large amorphous masses of pigment were scattered throughout all the sections. The malpighian corpuscles were small and widely separated, and the reticulum cells were few in number.

Pancreas: No pathological alteration was noted in any of the sections except that the islands of Langerhans were relatively few in number.

Kidneys: Both organs showed the same pathological alterations. There was a marked diffuse cloudy swelling of the epithelium of the tubules which in some areas was so marked as to be classified as complete atrophy. The glomeruli showed the same degenerative changes but to a far lesser extent. Amorphous masses of pigment were noted in the cytoplasm of the epithelial cells of the tubules and to a lesser extent in the glomeruli. Differential staining with Prussian blue showed this pigment to be almost entirely non-iron containing.

Lungs: Sections of the lungs showed no pathological alterations.

Central nervous system and peripheral nerves: The essential pathological alterations in the central nervous system were cytological. The cortical cells show marked pyknosis and in some areas vacuolization of the nuclei. Many showed no chromatin

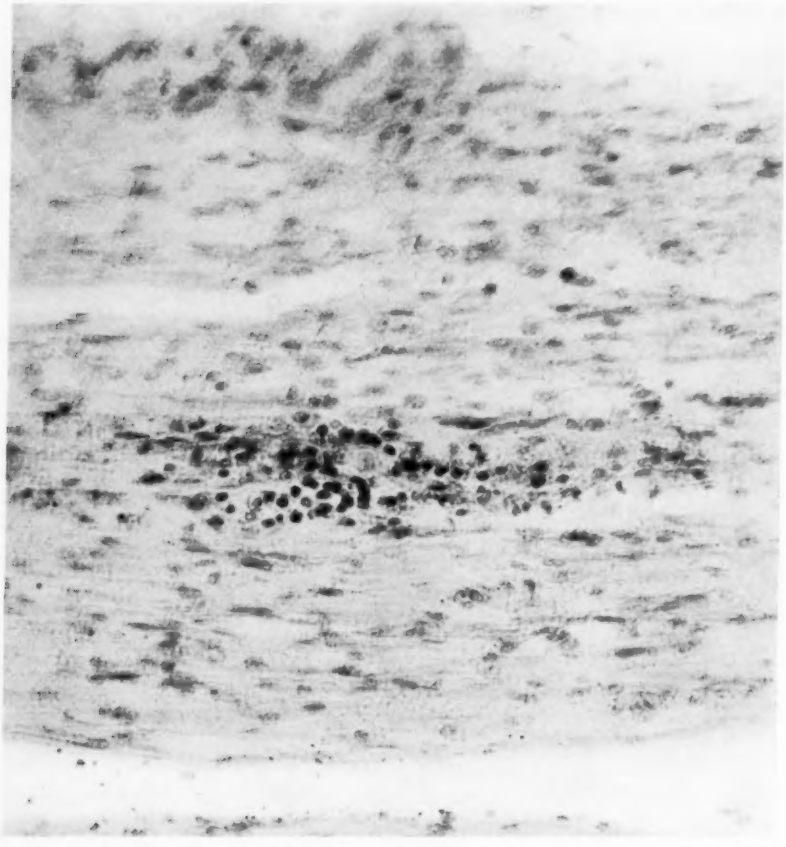

FIG. 5. Longitudinal section popliteal nerve showing round cell infiltration. Hematoxylin and eosin stain. Magnification × 280.

material and no nucleolus. Masses of amorphous pigment were noted in all sections, which by differential staining were shown to be iron and iron free pigment about equally divided. The motor cells of the anterior horns of the spinal cord and, to some extent, those of the posterior horns at all levels showed marked pyknosis and shrinking. Pigment was also found in all the sections of the cord examined, there being both iron and iron free pigment present. The Purkinje cells of the cerebellum showed definite signs of degeneration in that tigroid bodies were unstained or absent and many cells showed no staining of the nucleolus. The sections of the peripheral nerves showed in some areas marked degeneration of the myelin sheaths and in others extensive round cell infiltration. A few scattered phagocytic cells were noted which contained brown pigment.

Clinical Discussion

The onset in the acute cases, according to Mason,[5] is usually manifest by severe cramp-like pain in the abdomen, usually between the umbilicus and the pubis and occasionally radiating to the flanks, thighs or even to the chest. Usually there is a history of nervousness, easy fatigability, sleeplessness and vague abdominal pain preceding the initial attack by a few weeks or even a month. With the onset of abdominal pain, nausea and vomiting appear and constipation is the rule rather than the exception. Slight fever and moderate leukocytosis may be present. The abdomen is usually soft, but slightly tender to palpation. Roentgen-rays of the gastrointestinal tract show a dilated ileum, duodenum or a dilatation of some portion of the large bowel. With the advent of the acute attack the urine can be shown to contain urobilin, porphyrin and other pigments. The urine is a dark brown or burgundy wine color, giving a negative test for iron, and no erythrocytes are found in the sediment. Characteristic absorption bands for hematoporphyrin after the method of Garrod are found by spectroscopic examination. In the acute attacks ending fatally the nervous system shows definite involvement, with convulsions, states of delirium, and weakness of the extremities ending in an acute ascending paralysis with bulbar palsy and asphyxia. The disease occurs most commonly in the third and fourth decades although no age is exempt. The incidence is higher in women than in men, the ratio being about four to one. The prognosis in acute idiopathic hematoporphyria is extremely grave, 50 per cent dying with the first acute attack. In cases with involvement of the central nervous system the mortality is even higher.

In this case it is interesting to note that at no time during the acute illness was abdominal pain complained of nor was there abdominal distention or vomiting. Also death was not due to bulbar paralysis but undoubtedly resulted from toxemia, although bulbar symptoms were present for a time. The clinical picture of ascending paralysis here corresponds quite well with the toxic type of Landry's paralysis described by Drake [6] and others.

Pathological Discussion

The pathological findings in this case agree quite well with the findings of Mason, Courville and Ziskind [4] on their two autopsied cases except that they do not report enlargement of the spleen. The degenerative changes in the motor cells of the brain and spinal cord in this case would seem to be more advanced than their findings. The degenerative changes in the liver and kidneys would also seem to be more severe in this case. These differences might be explained by the fact that this patient lived about two months after the onset of the acute attack, whereas the duration of life in their cases from the advent of the acute attack was about one month. The degenerative changes in the Purkinje cells of the cerebellum and the changes in the myelin sheaths of the peripheral nerves with areas of round cell infiltration in the peripheral nerves are an almost exact counterpart of their findings.

Pathogenesis

The pathogenesis of acute idiopathic hematoporphyria is not well understood. Günther [1] contends that the condition is an inborn error of pigment metabolism whereby the normal synthesis of hemoglobin is interfered with, accompanied by

excretion of porphyrin in the urine. It is thought that the acute condition is a result of an endogenous or exogenous intoxication accompanied in all probability by a peculiar susceptibility to the disease.

Summary

A case of acute idiopathic hematoporphyria with symptoms of an acute ascending paralysis is presented with autopsy findings. Clinically the case presents neurological findings similar to the toxic type of Landry's paralysis. Death in this case was believed due to toxemia and not to bulbar paralysis and asphyxia which is the usual mode of termination in cases with extensive central nervous system involvement. The paralytic symptoms are accounted for by degenerative lesions of the anterior horn cells of the spinal cord and changes in the peripheral nerves.

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EDITORIAL

CERTAIN PROBLEMS CONNECTED WITH VOLUNTARY DISPENSARIES

Voluntary dispensaries have greatly increased in size and complexity in our larger cities in the last decade and constitute a very important factor in the medical care of urban communities. In spite of this fact, dispensaries have not received their proportionate share of attention from those interested in broad programs for public health. Yet all physicians and welfare workers realize that the unusual load placed upon dispensaries during recent years has rendered it urgent to find some solution for a number of old and fundamental problems connected with these institutions.

A first problem arises from the tendency of the dispensary to assume the rôle of family physician for its clients, when in fact its organization, and its relation to the other factors in medical care, i.e., home care and hospital care, are not adapted for this purpose. There is usually an attempt on the part of dispensaries to arrange matters so that the same physician will see the patient throughout one series of admissions, but even this is difficult to arrange and often proves impossible. Repeated readmissions of the patient over a period of years for varied conditions in different clinics usually mean that the patient's case is handled from many angles by many physicians in succession or even simultaneously. Too often such medical efforts lack coördination.

Very few dispensaries, indeed a negligible percentage, are linked with any system of home medical care. This is a very distinct handicap in that the dispensary physician has no chance to observe his patient's illness in the home. The crux of a diagnostic problem may, for example, be the nature of some nocturnal attack. The dispensary physician will never observe it because home care is not his province. Moreover, the dispensary physician will not meet the family of the patient, nor estimate the influence of his home environment on his illness.

Most dispensaries are linked with a hospital, but this association is usually more physical, administrative, and economic in nature than medical. With many notable exceptions, it is true that a wide gap usually exists between the dispensary staff and the house staff. Rarely has the dispensary staff much voice in the decisions made by the house staff concerning the former dispensary patient. There are too many patients and too little time in most institutions for such conferences. Frequently, moreover, the dispensary patient can not find a bed in the hospital linked with his dispensary and so is lost to view in another hospital.

The indigent patient frequently, therefore, receives such home care as he gets through the generosity of the practitioner in his neighborhood; goes to the dispensary as an ambulant case and there comes under various dispensary

physicians, and when he needs hospitalization is admitted to a hospital ward where still another group of physicians takes charge of his case. When he is discharged he may again apply for help to the local practitioner. It is obvious that the patient has received medical care in this circuit but it is also plain that he must often feel the need of a medical advisor who knows his whole medical history as well as his home environment. The lack of this steadying influence is one cause for the failure of the average dispensary and hospital system of medical care to deal successfully with the psychoneurotic patient. Even in the simpler problems of organic disease the present system is often a wasteful, repetitious and inefficient one.

Patients are at times admitted to the hospital who could be cared for in the home at much less expense if adequate home care were available; and often too, patients after discharge from the hospital may lose much of the value of their stay or at least have a greatly retarded convalescence for lack of any follow-up treatment.

A multiplicity of physicians and of examinations is often necessary for the adequate diagnosis of obscure disease but a single medical director is an essential factor in efficient treatment of illness.

It is widely acknowledged that better integration of these three phases of medical care is desirable. Partial solutions of many sorts have been evolved such as the unit system of records which keeps the patient's dispensary and hospital record together in one folder; the interchange of ward and dispensary attending physicians, dispensary work by interns and residents, and joint conferences of the two staffs. The medical social service worker evolved as an attempt to improve the physician's knowledge of the patient's home environment and to ensure more adequate carrying out of the instructions given as to treatment.

There remains, however, a fundamental inefficiency in the splitting up of responsibility for the patient's welfare entailed by the present relative isolation of dispensary medical care from home medical care and hospital medical care. In Boston, Buffalo, Minneapolis, and perhaps elsewhere integrated systems combining home, dispensary, and hospital care are in operation. They are deserving of careful study by other cities.

Another major problem involving dispensaries is their economic status. The budget of the average dispensary is made up roughly of the usual items for maintenance of the building and equipment, the cost of medical supplies, the salaries of non-professional personnel and a limited number of professional salaries. The bulk of the medical work, often all of it, is done without compensation by voluntary physicians. In addition there are often volunteer aides to the nursing and social service departments.

When voluntary dispensaries were smaller the voluntary hospital usually provided all the funds needed by the dispensary from its general income or from special gifts for this purpose. As the voluntary dispensaries grew in size the hospitals sought special appropriation for the free care given to patients in these units. But with considerable unanimity City and County

governments have failed to provide such support. In some cities Community Chests have given special support to dispensaries, but this is exceptional. In general, however, the support is derived about as follows: A small fee is charged all patients for admission and a further charge is made for medicines, roentgen-rays, etc. The fee is less than the usual charges for medical attention, special examinations, drugs, etc. and patients unable to pay are not turned away. In the Hospital Survey for New York the figure given for the average patient's fee in New York dispensaries is "about fifty cents" and it is estimated that this represents "about half of the cost to the institution of the service rendered, without including any item of expense for physicians' services." The deficit is paid by the hospital from its general funds.

There are at least two serious defects to this system. Partly because of the inclusion of part-pay patients as admissible clients the number applying for dispensary treatment has greatly increased. As a result the quality of the work tends to decrease. To avoid this danger the dispensary is driven to the appointment system, in other words, the dispensary turns some away.

The capacity of the dispensary to look after indigents is lessened since to survive financially a certain number of appointments must be given to part-pay patients. Moreover, such a system of admitting part-pay patients raises the problem of competition with the outside practitioner. Finally it demands of the voluntary dispensary physician not only that he shall care for the indigent without charge, but that he shall assist the hospital, by his professional work with part-pay patients, to earn money to support the dispensary in which he treats these indigents.

There is another aspect to the economic support of voluntary dispensaries which is equally unsatisfactory. The money received from patients is usually less than a half of the total money cost of the dispensary to the parent hospital. The rest must be found as a rule from general hospital receipts, just as the usual deficit on free ward cases must be found from these same receipts. Except in the cases of heavily endowed hospitals this means that the hospital must make sufficient profit on its private and semi-private accommodations to finance the deficit on the ward cases and on the dispensary. Part of the high cost of medical care in catastrophic illness, for people of moderate means, of which so much has been said, is due to the fact that such patients in many instances during their hospital stay pay not only for themselves but towards the cost of the wards and dispensaries. Medical care for the indigent is financed in part by what amounts to a special tax laid upon those already burdened with their own illness and its economic consequences.

A third problem arises which is connected with the teaching function of the dispensary. The clinical training of undergraduate students in the various clinics of medical school dispensaries is a well established function of these institutions. The training of the dispensary staff physician is often provided for in the best organized clinics. In smaller dispensaries, however, the Chief of Clinic, confronted with a scarcity of assistants and a large num-

ber of patients, is often forced to give all his available time to the examination of patients and has none left to devote to teaching of his assistants. Assistant physicians tend to drop out of clinics in which they do not get the educational benefit of consultation and conference on the problems presented by their patients. It is difficult to find in any city sufficient skilled clinicians with administrative and teaching ability to fill the positions as Chief of Clinic in the numerous clinics of each of the various dispensaries. This difficulty is not lessened by the disheartening lack of adequate facilities for the best work which prevails in a large number of impoverished dispensaries, nor by the fact that the position of Chief of Clinic in a dispensary rarely carries any salary. The potential rôle of the dispensary as a center of continuous postgraduate instruction is at present far from fully realized.

It seems evident that the dispensary, originally an emergency type of institution for palliative medicinal treatment of the sick poor, has vastly increased its clientele and the scope of its medical work, but that (1) the rôle that it should play in a system of medical care needs careful reconsideration; (2) its present inequitable system of financing should be abolished; and (3) its development as a postgraduate school for the practitioner should be planned and fostered.

M. C. P.

REVIEWS

Roentgen Technique. By CLYDE MCNEILL, M.D. 315 pages; 14.5 × 23.5 cm. Charles C. Thomas, Springfield, Illinois. 1939. Price, $5.00.

The positioning of a patient for a roentgen examination which most clearly demonstrates abnormalities, is an art developed by careful and patient effort, combined with a thorough knowledge of roentgen anatomy and pathology. The close supervision of roentgen technic by the roentgenologist makes for thorough diagnostic roentgenology which eliminates, to a high degree, the chance of error due primarily to faulty technic. The author is primarily concerned in this book with the positioning of the patient, but suggests other factors in the production of good diagnostic films. As far as possible such factors of technic as voltage, milliamperage, and exposure time are not discussed. These latter mentioned factors can be wisely disregarded in such a volume since they are constantly changing with the advent of new apparatus, and since they must be adjusted to the capacity of any given apparatus.

The author has arranged the material in a very concise and unique fashion. Generally speaking, there is a photograph of the patient positioned for the roentgen examination of a part in the upper half of the left hand page. Below this, is placed a neatly labelled drawing of the roentgenogram obtained. On the opposite page a list of some of the technical factors is presented followed by a detailed description of the position of the patient and the course of the central ray. With this description there is also a short discussion of the values and limitations of the particular position and in some instances, a list of references is furnished for those who wish to investigate further.

The book is quite complete, including such procedures as the visualization of the heart and great vessels by diodrast, cephalopelvimetry, lipiodol studies of the spine, and tonography.

The photographs and drawings are numerous and well reproduced. The paper and printing are excellent.

Dr. McNeill's work will be an asset to the library of anyone doing diagnostic roentgenology, and it is highly recommended for study, and as a reference.

W. L. K.

The Neurogenic Bladder. By FREDERICK C. MCCLELLAN, M.S., M.D. xvi plus 206 pages; 15 × 24 cm. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1939. Price, $4.00.

In recent years there has been such widespread interest in the physiology of the bladder that a monograph of this type is of particular value at this time. Anyone who has the time to search the English and American literature will, of course, find all that the book contains, but the author has presented a readable and practical summary of this extensive research.

In the early chapters the author discusses the anatomy and neurophysiology of the bladder. The spinal cord pathways are discussed, and he gives a very useful classification of the neurogenic bladder. The technic of cystometric study is clearly covered, together with a description of the various types of cystometers now in use. The concluding chapters deal with the treatment of the neurogenic bladder, and there is a very useful summary.

Five hundred cystometric studies were done by the author, and he has analyzed approximately 200 neurogenic bladders. The appendix includes a synopsis of 100 of these cases, and there are 49 graphs illustrating various types of bladder dysfunction. The bibliography consists of 118 well chosen titles. The book is to be highly recommended.

J. G. A., JR.

Medical Microbiology. By KENNETH L. BURDON, Ph.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University, School of Medicine. 763 pages; 15 × 23 cm. The Macmillan Company, New York. 1939. Price, $4.50.

This is an amplified edition of the author's "Textbook of Bacteriology." As is stated in the preface, it is the intention to reach fundamentals. For the pre-medical student it should be most valuable. To those who are studying nursing there is excellent material, but the book covers more of the intricacies of the subject than may be necessary in the short time allowed in their curricula. Its arrangement is unique and is most commendable, since the region of the body affected by the various microorganisms is emphasized. This is a marked improvement although it may seem arbitrary in certain cases. The usual textbook style is avoided. From many standpoints this book can be highly recommended.

J. G. McA.

Trauma and Internal Disease. By FRANK W. SPICER, A.B., M.D., F.A.C.P. 593 pages; 16 × 23 cm. J. B. Lippincott Co., Philadelphia. 1939. Price, $7.00.

This book collates and presents a new etiologic factor in internal medicine. As is necessary in such a pioneering work it brings together material from divergent sources. Many quotations and most examples have a legal tang. The quality gradient from example to example, and authority to authority is at times precipitous. The sections are compactly organized, with outlines and summaries for each chapter. To individuals engaged in medico-legal work this compilation will be of real help. The references are plentiful. To internists interested in acquiring a different perspective on their specialty it can be recommended.

C. A.

A Text Book of Bacteriology: The Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and the Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By HANS ZINSSER, M.D., Consulting Bacteriologist to the Peter Brigham Hospital and the Children's Hospital, Boston, and STANHOPE BAYNE-JONES, Professor of Bacteriology and Dean, Yale University Medical School, Master of Trumbull College, Yale University, New Haven, Conn. 990 pages; 17 × 25 cm. D. Appleton-Century Company, New York. 1939. Price, $8.00.

The eighth edition of this standard text bears definite marks of revision. Much of the older, out-of-date material has been omitted. A certain haziness in the phraseology here and there has been clarified. The authors have availed themselves of the opportunity to introduce much new material. Thus sulphanilamide and its action are discussed and the chapters on streptococci and the viruses, among others, show the handiwork of the reviser. The section on the protozoa has been omitted. The book will serve well its purpose as a text for students of medicine and public health.

F. W. H.

Man Against Himself. By KARL A. MENNINGER, M.D. 485 pages; 15 × 22 cm. Harcourt, Brace, and Company, New York. 1938. Price, $3.75.

Dr. Menninger's psychoanalytic study of self-destructive tendencies in man is divided into six sections. Each chapter is summarized. Like everything that Dr. Menninger writes, it is clear, extremely easy reading, and designed both for physicians and for the intelligent laity. It is a book that we can well imagine many patients reading with profit.

The first part takes up destruction in general; the second, the attitude toward suicide and the motives behind it; the third, various forms of chronic suicide such as

neurotic invalidism, alcohol addiction, and various types of behavior which increasingly cut the individual off from his social group; the fourth, focal suicide, deals with self-multilations, malingering, polysurgery, purposive accidents, and impotence and frigidity; part five is an extremely interesting discussion of chronic suicide, that is, the part that psychological factors play in the development and course of chronic disease; the sixth section deals with reconstruction, that is, therapeutic technics.

Dr. Menninger feels that all self-destructive attempts are motivated by a disturbance in the balance between primary constructive and destructive instincts, that is, between a life instinct and a death instinct. In all classes of acute, chronic, or subtotal suicide he finds in the individual a wish to kill or an aggressive component, a wish to be killed expressing a need for self-punishment, and a wish to die, all three colored by a distinct, ever-present erotic element.

Those persons who are opposed to psychoanalysis will find many statements to strengthen their opposition. There are many points in the theory which large numbers of people will find it impossible to accept since his evidence and, for that matter, the study itself, is purely a psychoanalytic one.

In various places in the book he takes up anthropological questions, giving taboos and customs of savage tribes in support of his arguments. This we find difficult to accept since after all savages are integrated with their own civilizations, whereas the distinguishing feature of the psychotic individual in any social group is his failure to integrate himself with that group. In dealing with "organic suicide," he summarizes by saying, "Some forms of organic disease represent structuralization of perverted functions forced upon these organs to solve unconscious conflicts, the nature of these conflicts being related to the opposition and interaction of aggressive, self-punitive, and erotic components of the self-destructive tendency. The hypothesis is that organic lesions, so frequently requiring as they do direct agents from the environment such as bacteria or trauma for their initiation, differ not only in this respect but also in certain psychological respects from so-called functional disorders, mainly in that the sacrifice demanded by the destructive tendencies is a greater one and that the conflict is more strongly and deeply repressed, i.e., less accessible to consciousness."

Of the several studies of suicide which have appeared recently we find in this more food for thought than in any of the others. It is well worth reading.

H. M. M.

COLLEGE NEWS NOTES

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1940–41, are herewith announced and published:

President-Elect ..... Roger I. Lee, Boston, Mass.
First Vice President ..... Robert A. Cooke, New York City
Second Vice President ..... James G. Carr, Chicago, Ill.
Third Vice President ..... Henry M. Thomas, Jr., Baltimore, Md.

The election of nominees shall be by the members of the College at its Annual Business Meeting, Cleveland, Ohio, April 4, 1940. These nominations do not preclude nominations made from the floor at the Annual Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,
CHARLES E. WATTS, Seattle, Wash.,
JAMES J. WARING, Denver, Colo.,
CLARENCE L. ANDREWS, Atlantic City, N. J.,
WILLIAM J. KERR, San Francisco, Calif.,
SYDNEY R. MILLER, *Chairman*, Baltimore, Md.,
Committee on Nominations

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership and their Initiation Fees and Life Membership payments have been added to the permanent Endowment Fund of the College:

Dr. Anthony Bassler, New York, N. Y.
Dr. Samuel A. Brown, New York, N. Y.
Dr. George B. Crow, Burlington, Iowa
Dr. Horace K. Richardson, Stockbridge, Mass.
Lt. Comdr. Thomas F. Duhigg, (MC), U. S. Navy
Dr. William S. Kerlin, Shreveport, La.
Dr. Charles T. Way, Cleveland, Ohio

The Life Membership plan of the College, whereby members may underwrite their future dues during their productive years, is both equitable and practicable. It offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. To date, January 31, 1940, 128 physicians have become Life Members. Life Membership fees may be deducted on income tax returns.

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of a gift of the 3rd edition, "Pharmacology, Materia Medica and Therapeutics," by the author, Dr. Charles Solomon (Associate), Brooklyn, N. Y.

Donations of books by members of the College have resulted in the building up of a most interesting and worthwhile Library of books dealing primarily with Internal Medicine and its allied specialties. These books serve a definitely useful purpose.

The following donations of reprints are also acknowledged since the last report:

Dr. Maurice J. Abrams (Associate), Brewton, Ala.—1 reprint;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—5 reprints;
Dr. George Warren Burnett (Associate), Baltimore, Md.—2 reprints;
Dr. Joseph F. Elward (Associate), Washington, D. C.—3 reprints;
Dr. J. O. Finney (Associate), Gadsden, Ala.—2 reprints;
Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif.—19 reprints;
Dr. Glenville Giddings, F.A.C.P., Atlanta, Ga.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Crawford R. Green, F.A.C.P., Troy, N. Y.—1 reprint;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—9th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";
Dr. Hartwell Joiner, F.A.C.P., Gainesville, Ga.—1 reprint;
Dr. David W. Kramer, F.A.C.P., Philadelphia, Pa.—6 reprints;
Dr. A. B. McCreary (Associate), Jacksonville, Fla.—1 reprint;
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—2 reprints.

Regional Meeting of Eastern Pennsylvania Members

Under the Governorship of Dr. Edward L. Bortz, Fellows and Associates of the College residing in eastern Pennsylvania held their second annual "Round-Up" at Philadelphia, February 9, 1940. A buffet luncheon was served at the College Home, 4200 Pine St., followed by a scientific program at the Medical Laboratories of the University of Pennsylvania.

1. "Clinical Uses of Intestinal Intubation," Dr. W. Osler Abbott, Philadelphia.
2. "Non-Hypoglycemic Coma Incident to Insulin Treatment of Schizophrenia," Dr. Kenneth Appel and Dr. Lauren H. Smith, Philadelphia.
3. "The Prognostic Value of the Electrocardiogram," Dr. Jesse Lenker, Harrisburg.
4. "Gastroscopy," Dr. Louis Clerf, Philadelphia.
5. "Management of Hyperthyroidism," Dr. Stanley Conklin, Sayre.
6. "Vitamin Accomplishments," Dr. John Willard, Philadelphia.

In the evening a dinner was given at the Penn Athletic Club, where Dr. Harry B. Wilmer, F.A.C.P., and members of the Philadelphia Orpheus Club provided entertainment. Among those who addressed the dinner meeting were Dr. William D. Stroud, Treasurer; Dr. O. H. Perry Pepper, President; and Mr. E. R. Loveland, Executive Secretary.

There was a large and representative attendance of the College members from eastern Pennsylvania, with a number of the Governors of the College from neighboring states also present as guests.

Dr. Graham Asher, F.A.C.P., Kansas City, Mo., recently was awarded first prize for the best scientific exhibit at the annual meeting of the Southern Medical Association. His exhibit was of a machine which visualizes the beating of the human heart on a fluorescent screen, keeping it visible for at least fifteen seconds. It is said

that heart conditions can be diagnosed by watching this record. The fluorescent film may be kept as a permanent record.

Major General Charles R. Reynolds, F.A.C.P., retired Surgeon General of the U. S. Army, has accepted an appointment as Director of the newly created Bureau of Tuberculosis Control for the State of Pennsylvania and has his headquarters at Harrisburg. Among members of an advisory committee appear the names of Dr. Burgess Gordon, F.A.C.P., Philadelphia; Dr. Robert G. Torrey, F.A.C.P., Philadelphia; Dr. Charles Howard Marcy, F.A.C.P., Pittsburgh; Dr. Charles H. Miner, F.A.C.P., Wilkes-Barre; and Dr. William Devitt, F.A.C.P., Allenwood.

American Physicians Art Association

The annual exhibit of the American Physicians Art Association will be held at the Belmont-Plaza Hotel, New York City, June 9–15, at the same time as the annual session of the American Medical Association. The entire top floor of the hotel will be utilized by the Physicians Art Association. The New York Physicians Art Club will act as hosts. Details of the exhibit plans may be obtained from Dr. Abraham Wolbarst, 114 East 61st Street, New York City, or from the President, Dr. Henry N. Moeller, 327 Central Park West, New York City.

Six members of the editorial board of the North Carolina Medical Journal are Fellows of the American College of Physicians:

Dr. Paul P. McCain (Chairman), Sanatorium;
Dr. W. Reece Berryhill, Chapel Hill;
Dr. C. C. Carpenter, Wake Forest;
Dr. Frederic M. Hanes, Durham;
Dr. Paul H. Ringer, Asheville;
Dr. Wingate M. Johnson (Editor), Winston-Salem.

Dr. Otis G. King (Associate), Bluefield, W. Va., is President of the Mercer County (West Virginia) Medical Society for the current year.

The North Carolina Neurological and Psychiatric Association held its annual meeting at Charlotte, N. C., January 26, 1940. Dr. Mark Griffin, F.A.C.P., Asheville, is Vice President of the organization and Dr. Archie A. Barron, F.A.C.P., Charlotte, was the program chairman. Dr. Barron led a round table discussion on "Acute Infectious and Suppurative Conditions of the Brain and Spinal Cord—Sulfanilamide, etc."; Dr. Kenneth E. Appel, F.A.C.P., Professor of Psychiatry at the University of Pennsylvania, Philadelphia, presented a paper on "Frontiers in Psychological Medicine"; and Dr. Mark Griffin, F.A.C.P., Asheville, was one of those who discussed a paper on "Neurological Heredity in North Carolina."

At the Methodist Hospital of Brooklyn, N. Y., Dr. Frank Bethel Cross, F.A.C.P., has been appointed Chief Attending Physician; Dr. Alexis T. Mays, F.A.C.P., Senior Attending Physician; and Dr. Irving L. Cabot, F.A.C.P., Attending Physician.

Dr. Ira A. Darling, F.A.C.P., resigned as Superintendent of the Springfield State Hospital (Sykesville, Md.) January 14, 1940, to accept the position of Superintendent of the Torrance State Hospital (Torrance, Pa.), January 15, 1940.

Dr. Francis R. Dieuaide, F.A.C.P., for some time Professor of Medicine and Head of the Department of Medicine at Peiping Union Medical College, Peiping, China, has accepted an appointment as of January 1, 1940, as Associate Professor of Medicine in Harvard University Medical School and Physician to the Massachusetts General Hospital.

Dr. David W. Kramer, F.A.C.P., Philadelphia, Pa., was recently appointed Visiting Physician to the Medical Division of the Philadelphia General Hospital and Assistant Physician on Medical Services A and B of the Jefferson Hospital.

The Resident and Consulting Staff of the City Sanitarium of St. Louis recently elected Dr. J. R. Nakada, F.A.C.P., as President of the Staff for 1940. Dr. Nakada acted as Vice President during 1939. He has also been elevated to the Staff of Consulting Internists of Missouri Baptist Hospital.

Dr. James L. Wade (Associate) Parkersburg, W. Va., was recently elected President of the Academy of Medicine of Parkersburg.

Dr. Wade addressed the Presidents' and Secretaries' Conference of the State Medical Association in Charleston, January 6, on "Development of Public Relations by County Medical Societies."

The sixth annual meeting of the Mississippi Valley Medical Society will be held at Rock Island, Ill., September 25 to 27, 1940. The meeting will consist largely of practical instruction courses. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., is the Secretary-Treasurer. Among the Society's Board of Directors are Dr. Nathan S. Davis, III, F.A.C.P., Chicago; Dr. F. G. Norbury, F.A.C.P., Jacksonville; and Dr. D. G. Stine, F.A.C.P., Columbia.

Dr. James G. Carr, F.A.C.P., Chicago, Secretary and Professor of Medicine, Northwestern University School of Medicine, was the 1939 recipient of the Distinguished Service Award of the Mississippi Valley Medical Society, "in recognition of his innate sincerity, his deep understanding of medical problems, his kindly ministrations, with a fine basic personality."

Western Reserve University School of Medicine recently announced a grant of $6,000 by the John and Mary R. Markle Foundation, in continuation of investigations on methods of revascularizing the heart after coronary obstruction.

The University also announces a grant of $1,250 from the National Research Council to support from January 1 to June 30, 1940, a study of human ovulation under the direction of Dr. William W. Greulich, Professor of Physical Anthropology and Anatomy and Director of the Brush Foundation.

The American Association for the Study of Goiter again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association, which will be held at Rochester, Minn., on April 15, 16 and 17, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten, double spaced copy sent to the Corresponding Secretary, Dr. W. Blair Mosser, 133 Biddle St., Kane, Pa., not later than March 15.

Dr. William W. Cadbury, F.A.C.P., Superintendent of the Canton (China) Hospital, is Chairman of the Executive Committee of the Canton International Red Cross. This organization has 43 stations where food or medical relief is given to refugees and sufferers. Among the activities listed in its latest report are:

Over 4000 refugees in four camps;
Over 70,000 meals served every week from 28 feeding centers;
Over 10,000 dispensary treatments weekly;
Nearly 50,000 quinine pills given out in the last month;
Medical supplies distributed freely to hospitals in the city and to 24 towns and villages outside;
Doctors procured for needy places;
General Medical Service to civilian population and to refugee camps;
30,000 inoculations for cholera and many smallpox vaccinations;
Assistance rendered to four orphanages;
5,000 inmates of Government institutions assisted.

Dr. Cadbury recently returned on leave to Moorestown, N. J.

Dr. O. Costa Mandry, F.A.C.P., San Juan, is Chairman of the Editorial Board of the Puerto Rico Health Bulletin, which is edited and published by the Insular Department of Health.

The thirty-sixth Annual Congress on Medical Education and Licensure was held at Chicago, February 12 and 13, 1940. Dr. John H. Musser, F.A.C.P., New Orleans, presided at one of the afternoon sessions, at which Dr. Nathan B. Van Etten, F.A.C.P., President-Elect of the American Medical Association, New York City, presented a paper on "Program for the Instruction of Interns," and Rear Admiral Ross T. McIntire, Surgeon General of the U. S. Navy, Washington, D. C., presented a paper on "Medical Education in Relation to the Naval Service."

Dr. Alan Brown, F.A.C.P., Professor of Pediatrics on the University of Toronto Faculty of Medicine, presented a paper on "The Rôle That a Children's Hospital Should Play in the Community."

The Federation of State Medical Boards was addressed by Dr. Van Etten and formal papers were presented by the following:

Dr. Joseph H. Pratt, F.A.C.P., Boston, "The Refugee Physician";
Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, "Inter-American Relation in Medical Education and Licensure";
Dr. Willard C. Rappleye, F.A.C.P., New York City, "Advisory Council on Medical Education as Related to Licensure."

Dr. Nathan B. Van Etten, F.A.C.P., New York City, spoke on "Medical Care and the Medical Profession" January 9 in connection with the De Lamar Foundation of the Johns Hopkins University School of Hygiene and Public Health at Baltimore.

Dr. J. Murray Kinsman, F.A.C.P., Louisville, Ky., recently addressed the Evanston Branch of the Chicago Medical Society on "Present Status of Sulfapyridine."

Dr. William B. Castle, F.A.C.P., Professor of Medicine, Harvard University Medical School, Boston, was awarded the Walter Reed Medal at a meeting of the American Society of Tropical Medicine in Memphis, Tenn., November 21. The citation states that the award was made in consideration of his "meritorious achievements in the field of tropical medicine, his outstanding leadership and scientific investigations which have resulted in most important additions to our knowledge of sprue and related anemias." The award is given only in years when there has been particularly outstanding work. The medal had not been awarded during the past four years.

Dr. Castle was awarded the John Phillips Medal of the American College of Physicians for 1933.

It was recently announced that Dr. Martin A. Mortensen, F.A.C.P., Santa Monica, Calif., would return as a member of the staff in internal medicine of the Battle Creek Sanitarium, Battle Creek, Mich.

Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, President of the Michigan State Medical Society, addressed the Wayne County Medical Society at Detroit on December 4 on "The Function of the State Medical Society."

Dr. Soma Weiss, F.A.C.P., Hersey Professor of the Theory and Practice of Physics at Harvard University Medical School, is Chairman, and Dr. Sidney Burwell, F.A.C.P., Dean of the Medical School, and Dr. William B. Castle, F.A.C.P., Professor of Medicine, are ex officio members of a committee on pharmacotherapy recently established at Harvard University to develop research and improve graduate training in the field of pharmacology and experimental therapeutics, coördinating the efforts of practicing physicians and Harvard scientists in biology, chemistry and medicine. It is said that a group of corporations interested in medical and therapeutic research will supply the funds to support the work of the committee for the next five years.

Dr. Walter Baumgarten, F.A.C.P., St. Louis, has been elected Editor of the Journal of the Missouri State Medical Association.

The November-December issue of the Review of Gastroenterology was dedicated to Dr. Anthony Bassler, F.A.C.P., New York, in honor of his sixty-fifth birthday. For the past four years Dr. Bassler has been President of the National Gastroenterological Association. He is the author of several books in his specialty and has made many contributions to medical journals. At present he is consulting gastro-enterologist to several hospitals in New York City and environs.

Dr. Maxwell Finland, F.A.C.P., Boston, addressed the Cincinnati Academy of Medicine December 5 on "Serotherapy and Chemotherapy of Pneumonia."

Dr. Wallace M. Yater, F.A.C.P., College Governor for the District of Columbia, Washington, D. C., addressed a joint meeting of the Medical Society of the District

of Columbia and the Baltimore City Medical Society December 1 in Baltimore on "Pathogenesis and Prognosis of Bundle Branch Block."

Dr. Raymond Hussey, F.A.C.P., Baltimore, has been appointed chairman of a state medical board for occupational diseases by the Governor of Maryland.

Among lecturers in a series of free public meetings on medical subjects, which began January 7 at Harvard University Medical School, were the following:

Dr. Chester M. Jones, F.A.C.P., January 7, "Digestion and Indigestion";
Dr. Chester S. Keefer, F.A.C.P., January 21, "What About Sulfanilamide?";
Dr. Paul D. White, F.A.C.P., February 4, "Facts and Fancies About Heart Disease";
Dr. William B. Breed, F.A.C.P., March 10, "Health in Middle Age."

Dr. David M. Cowie, F.A.C.P., Ann Arbor, has been reëlected Secretary of the Michigan Pediatric and Infectious Disease Society.

Dr. Priscilla White, F.A.C.P., Boston, addressed the Camden County (N. J.) Medical Society at Camden, N. J., December 5, on the subject of diabetes.

Dr. William H. Ross, F.A.C.P., Brentwood, was honored recently by the Suffolk County (N. Y.) Medical Society at a dinner in recognition of his fifty years of medical practice. Among those who offered tributes to Dr. Ross was Dr. Peter Irving, F.A.C.P., New York, Secretary of the New York State Medical Society. Dr. Ross, now seventy-seven years of age, was formerly president of the state medical society, the Associated Physicians of Long Island, the Suffolk County Medical Society and the New York Association of Superintendents and Managers of Tuberculosis Sanatoria.

Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., addressed the New York Academy of Medicine December 7 on "Clinical Aspects with Respect to the Venous System."

Dr. Edwin C. Swift, F.A.C.P., and Dr. Arthur J. Logie (Associate), both of Jacksonville, Fla., were recently elected Vice Presidents of the Florida East Coast Medical Association.

Dr. Hugh R. Butt (Associate), Rochester, Minn., addressed the North Shore Branch of the Chicago Medical Society January 2 on "Vitamins, Recent Advances and Their Clinical Application."

Dr. Emanuel Libman, F.A.C.P., New York City, delivered the fifth annual Martland Lecture before the Essex County (N. J.) Anatomical and Pathological Society, Newark, January 24, on "Endocarditis."

Dr. Alvan L. Barach, F.A.C.P., New York City, addressed the International Spanish Speaking Association of Physicians, Dentists and Pharmacists during December on "Modern Treatment of Asthma."

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., participated in a symposium on "Chemotherapy Including Sulfapyridine and Allied Compounds" at the annual meeting of the New York Academy of Medicine January 4.

Dr. Albert B. McCreary (Associate), Jacksonville, State Health Officer for Florida, was recently elected President of the Florida Public Health Association.

It was recently announced that Dr. Walter H. Baer (Associate), formerly Superintendent of the Peoria (Ill.) State Hospital, has been appointed Acting Superintendent of the Manteno (Ill.) State Hospital.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, addressed the Golden Belt Medical Society, Salina, Kan., January 4, on "Endocrinology in General Practice."

Dr. David W. Gillick, F.A.C.P., Superintendent and Physician-in-Charge of the Shawnee (Okla.) Indian Sanatorium, has been appointed Medical Director for District No. 5 of the Indian Medical Service.

Dr. Orville E. Egbert, F.A.C.P., El Paso, Tex., was recently installed as President of the Southwestern Medical Association.

Dr. Roscoe L. Sensenich, F.A.C.P., South Bend, Ind., Dr. Henry R. Carstens, F.A.C.P., Detroit, and Dr. Hilton S. Read, F.A.C.P., Atlantic City, N. J., were speakers at the fourteenth annual meeting of the National Conference on Medical Service held at Chicago February 11.

Dr. James F. McFadden, F.A.C.P., and Dr. John Zahorsky, F.A.C.P., were among members of the Faculty of St. Louis University School of Medicine who were recently honored at a dinner sponsored by the Women's Club of the School of Medicine. The dinner was given in recognition of all of those who had served 25 years on the Faculty. Replicas of the seal of the university were presented to each guest of honor

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Dr. Cornelius P. Rhoads, F.A.C.P., New York City, addressed the New York Pathological Society January 25 on "Aplastic Anemia."

Dr. Martha Tracy, F.A.C.P., Dean of the Woman's Medical College of Pennsylvania, has been made Assistant Director of Public Health of Philadelphia. She will continue as Dean of the Medical College until the end of the present academic year or until a successor is elected.

Dr. Tracy received her medical degree from the Woman's Medical College of Pennsylvania in 1904 and the degree of doctor of public hygiene from the University of Pennsylvania in 1917. She has been associated with the Woman's Medical College since 1913, first as Professor of Physiologic Chemistry (1913–21), then as Professor of Hygiene (1921–23), then as Professor of Preventive Medicine (1923–31) and as Dean since 1918. She has been a member of the Philadelphia Board of Health since 1936.

Dr. Oscar Lotz, F.A.C.P., Milwaukee, has been elected Executive Secretary of the Wisconsin Anti-Tuberculosis Association.

The American Social Hygiene Association held its twenty-seventh annual meeting at Chicago, February 1–2. Among speakers were Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service; Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., "Adequacy of Preparation—Are We Giving Physicians the Training and Technics They Need?"; and Dr. Rock Sleyster, F.A.C.P., President of the American Medical Association, Wauwatosa, Wis., "Rôle of the Private Physician—How Can He Strengthen the Control Program?"

Major General Merritte W. Ireland, F.A.C.P., former Surgeon General of the U. S. Army, was awarded the William Freeman Snow Medal on behalf of the Association.

The midwinter postgraduate clinics of the Colorado State Medical Society were held at Denver, February 7 to 9. Among guest speakers was Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "Present Status of Our Knowledge Concerning the Treatment of the Anemias."

Among guest speakers on the program of the third annual Atlanta Graduate Medical Assembly, January 15, under the auspices of the Fulton County (Ga.) Medical Society, the following were included:

Dr. William E. Chamberlain, F.A.C.P., Philadelphia, "Pitfalls in X-Ray Diagnosis";
Dr. Philip S. Hench, F.A.C.P., Rochester, Minn., "Chronic Infectious (Atrophic) Arthritis; Its Diagnosis and Treatment";
Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "The Prognosis and Treatment of Hypertension."

At the Indiana State Medical Association's annual conference of secretaries of county medical societies, held at Indianapolis, January 21, Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spoke on "Postgraduate Medical Education in Oklahoma," and Dr. Peter Irving, F.A.C.P., New York City, spoke on "Hospital Insurance and Medical Indemnity."

Dr. George R. Minot, F.A.C.P., Professor of Medicine, Harvard University Medical School, Boston, was awarded the Gordon Wilson Medal of the American Clinical and Climatological Association at its last meeting.

Dr. J. Arthur Myers, F.A.C.P., Professor of Medicine, Preventive Medicine and Public Health at the University of Minnesota Medical School, Minneapolis received the 1939 gold medal of the Society of Puerto Rican Tuberculosis Physicians for "outstanding work in the field of Tuberculosis." Dr. Myers addressed the annual session of the Puerto Rico Medical Association and gave a series of lectures under the auspices of the Society of Puerto Rican Tuberculosis Physicians during December, 1939.

Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., has succeeded Dr. Moses Barron, F.A.C.P., Minneapolis, Minn., as President of the Minnesota Society of Internal Medicine.

Dr. Grant Thorburn, F.A.C.P., New York City, delivered an address on tuberculosis February 6 before the Essex County (N. J.) Medical Society at Newark.

Dr. Robert F. Loeb, F.A.C.P., New York City, is Chairman of the Committee, and Dr. I. Ogden Woodruff, F.A.C.P., New York City, is a member, appointed by Dr. S. S. Goldwater, Commissioner of Hospitals of New York City, to assist in the selection of a medical staff for the new five-hundred bed hospital for tuberculosis soon to be completed. Applicants for appointments must be citizens of the United States and must be licensed to practice in New York. The superintendent, roentgenologist and pathologist will be appointed from civil service lists.

Dr. John H. Skavlem, F.A.C.P., Cincinnati, has been appointed Acting Medical Director of the Hamilton County (Ohio) Tuberculosis Sanatorium, following the resignation of Dr. Kennon Dunham, F.A.C.P., Cincinnati, who has been associated with the Sanatorium since 1910.

At the December meeting of the American Association for the Advancement of Science, Dr. Edmund Jacobson, F.A.C.P., announced a new instrument—The Integrating Neurovoltmeter—to afford the direct measurement of nervous or of muscular states in various diseases, without anesthetic.

On October 24, 1939, a meeting was held at the St. Louis Medical Society in honor of Dr. William Washington Graves, Professor of Neuropsychiatry, St. Louis University School of Medicine. At this meeting, Dr. Graves was awarded a Certificate of Merit and a Gold Medal for scientific accomplishment in his classification of scapulae and other inherited characters, and of his discovery of "The Age-Incidence Principles of Investigation."

The St. Louis Medical Society has given this Certificate of Merit for scientific accomplishment on only two occasions before Dr. Graves received it.

The first was given to Dr. Evarts A. Graham and his associates, Drs. Glover H. Copher, Warren H. Cole and Sherwood Moore, June 7, 1927, for their work in cholecystography. The second was given to Dr. Edward A. Doisy, March 19, 1935, for his achievements in hormone chemistry and physiology.

During the twentieth annual meeting of the American Student Health Association at the Hotel New Yorker, New York, December 28 and 29, 1939, a luncheon session was devoted to the subject of tuberculosis among college and university students. Presiding was Dr. Kendall Emerson, managing director of the National Tuberculosis Association. Fellows of the College who took part in the meeting included Dr. J. Burns Amberson, Jr., Professor of Medicine, Columbia University, who spoke on "Dividends from a Tuberculosis Control Project among Students"; Dr. Herbert R. Edwards, director of the Bureau of Tuberculosis, New York City Department of Health, who discussed the paper; and Dr. Charles E. Lyght, director of the Student Health Service, Carleton College, Northfield, Minnesota, who presented the ninth annual Report of the Tuberculosis Committee.

OBITUARIES

DR. CHARLES ANDREW RAY

Dr. Charles Andrew Ray, F.A.C.P., Charleston, W. Va., died January 21, 1940, of a heart attack.

Dr. Ray was born in Charleston, W. Va., May 14, 1864, and received his early education in the public schools and high school of Milton, W. Va. He received his degree of Doctor of Medicine from the College of Physicians and Surgeons (Baltimore) in 1887 and served his internship at the Baltimore City Hospital. Later, he took postgraduate work at Johns Hopkins University School of Medicine and at the New York Polyclinic Medical School and Hospital. In 1917, he began the practice of medicine in Charleston.

Dr. Ray was a member of the Kanawha County Medical Society, serving as President in 1925; the West Virginia State Medical Association, serving as President in 1928; the Tri-State Medical Society, the Southern Medical Association, the American Medical Association and a Fellow of the American College of Physicians since 1926. He was Editor-in-Chief of the West Virginia Medical Journal in 1927 and continued to serve as Associate Editor of this Journal until 1938. He was Chief of the Medical Staff and Instructor to the Nurses Training School of the Kanawha Valley Hospital and President of the County Court of Kanawha County at the time of his death.

"As a man of unfaltering courage, of understanding and of rare good humor, Dr. Ray exemplified all of the finest attributes of a noble profession."

ALBERT H. HOGE, M.D., F.A.C.P.
Governor for West Virginia

DR. ALBERT W. NELSON

Albert William Nelson was born in Owatonna, Minn., January 20, 1878, and died in a local hospital in Battle Creek of a stroke of apoplexy January 5, 1940. His family moved to Battle Creek during his boyhood and he attended Battle Creek College, obtaining his B.S. degree in 1898. After four years' training he graduated with his M.D. from the American Medical Missionary College in 1903 and at once joined the Sanitarium Medical Staff with which he served until 1920, when he entered private practice and at the same time was on the medical staff of the Maple Street Hospital until it closed in 1930. Dr. Nelson was a Fellow of the American College of Physicians and Member of the Calhoun County and State Medical Society and a Fellow of the American Medical Association. Soon after his graduation the doctor spent some time doing postgraduate work in Baltimore. In 1936 he did postgraduate work at Washington University School of Medicine in St. Louis, in 1937 Cook County Hospital, Chicago, and in 1938 the

University of Buffalo School of Medicine, these courses running from two to three weeks. He was a quiet, dignified Christian gentleman and always enjoyed an excellent practice. Dr. Nelson's medical work was also his mission and hobby and he never failed to answer a call with no thought of whether there would be a fee. His first apoplectic stroke was on June 3, 1939, which was comparatively light and from which he slowly made a very fair recovery and was able for several months to attend his office and see patients daily. He did not recover consciousness from the final stroke and passed on within a few hours. He was unmarried and left behind a sister, Miss Mable Nelson, and two paternal aunts and one uncle, too far distant to attend the funeral which was crowded with friends and former patients.

A. B. Olsen, M.D., F.A.C.P.,
Battle Creek, Michigan

DR. MARTIN LUTHER STEVENS

Dr. Martin L. Stevens was born in Thornville, Ohio in 1864. He graduated in medicine from the University of Maryland (Baltimore Medical College) in 1891. After several years in general practice, Dr. Stevens joined the staff of the Winyah Sanatorium in Asheville, remaining in association there until 1901, when he established himself in private practice. He limited his work to internal medicine, specializing in tuberculosis, and was active in it until his sudden death, while dressing, on the morning of January 20, 1940, apparently from a coronary occlusion.

Dr. Stevens' interest in medical societies was continuous throughout his career. He was senior honorary member of the Buncombe County Medical Society, a Fellow of the North Carolina State Medical Society (President, in 1932), a member and past President of the North Carolina Board of Medical Examiners, charter member of the National Tuberculosis Association, as well as a member of the North Carolina State Tuberculosis Association, the Southern Tuberculosis Conference, and a corresponding member of the International Tuberculosis Conference, as well as a member of the American Clinical and Climatological Association, the Southern Medical Association, and of the American Medical Association, being a member of the House of Delegates from 1924 until his death. He became a Fellow of the American College of Physicians in 1929, and was a diplomate of the American Board of Internal Medicine.

Dr. Stevens was a loyal and constant attendant at medical meetings, but by reason of his modest and retiring disposition rarely participated on the floor in discussions. In his earlier years, however, he was the author of quite a few articles on tuberculosis. During the World War, he was Chairman of the Medical Advisory Board, having supervision of the western counties of the state.

He was a devoted, active member of St. Mark's Lutheran Church of Asheville, as well as a member of the National Council of his church, and a

member of the Rotary Club. He was a member of the staffs of various tuberculosis sanatoria and hospitals of the city, being Chief of Staff of St. Joseph Hospital in 1939. He was a member of the Board of Directors of the Western Carolina Tuberculosis Sanatorium, which institution he visited only a few hours previous to his death.

Dr. Stevens left no children, but he is survived by his widow, Mrs. Lula Mary Patterson Stevens, whom he married in 1894.

In spite of an unusual degree of modesty and a very retiring disposition, Dr. Stevens was signally honored by his colleagues with positions of honor and trust, all of which he discharged with fidelity and sincerity. He maintained his interest, as well as failing strength of later years permitted, in all medical societies and felt a keen interest in the American College of Physicians, whose meetings he attended whenever possible. In his passing, the medical profession of his community and state, as well as a larger sphere of friends and acquaintances reached through his broad reputation, will miss a faithful, loyal and fine friend.

C. H. Cocke, M.D., F.A.C.P.,
Governor for North Carolina

DR. JOHN CONOVER CLAYTON

John Conover Clayton, F.A.C.P., Freehold, N. J., died of coronary thrombosis on November 25, 1939, at the Princeton Hospital. He was born at Princeton, N. J., February 25, 1882, where his early life was spent, and from which place he went to Lawrenceville School, whence he was graduated in 1901. He spent the next two years in Princeton University, and then matriculated at the University of Pennsylvania School of Medicine, being graduated in 1907. The next two years were passed in internships at the Naval Hospital, Washington, D. C., and the Manhattan State Hospital, New York, N. Y.

In 1909, Dr. Clayton began general practice in Freehold, N. J., where he lived and carried on his profession until his death. He became especially interested in circulatory diseases, and, at the age of 38, began postgraduate work in cardiology at the New York Post-Graduate Medical School and Hospital, where he continued for two years. He became the Attending Cardiologist at the Fitkin Memorial Hospital, Neptune, N. J., and at the Riverview Hospital, Red Bank, N. J. He was, at one period, Attending Physician to the Ann May Hospital at Spring Lake, N. J.

Dr. Clayton was a past President and Secretary of the Monmouth County Medical Society, a member of the Medical Society of New Jersey, Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

Beside being a leader in his profession, Dr. Clayton took an active interest in both church and civic affairs. His chief hobbies were golf and

football, and it was at the Navy game at Princeton that he suffered the illness of which he died a few hours later in the Princeton Hospital.

GEORGE H. LATHROPE, M.D., F.A.C.P.,
Governor for New Jersey

DR. CHARLES WALTER STONE

On December 9, 1939, Dr. Charles Walter Stone, F.A.C.P., died at Cleveland, Ohio, after an illness of more than a year.

Born in Pittsburgh, Pa., in 1879, he attended school in that city and was graduated from Washington and Jefferson College with the degree of A.B. He studied medicine at Johns Hopkins University and received his degree of Doctor of Medicine in 1905. He served as intern on the Medical Service at the Lakeside Hospital in Cleveland from 1905 to 1906. After this, Dr. Stone became resident in medicine at Lakeside Hospital under Dr. C. F. Hoover and Dr. E. F. Cushing. Following his years of resident service at Lakeside Hospital, Dr. Stone studied in France, Germany, and England. His postgraduate studies were entirely in Neurology and Psychiatry. Then he returned to Cleveland and entered the practice of Neurology and Psychiatry. He became one of the outstanding specialists in Neuro-Psychiatry in Cleveland.

Always interested in the academic angle of his chosen specialty, he held numerous leading posts in the Medical Department of Western Reserve University, eventually filling the post of Associate Clinical Professor of Nervous and Mental Diseases. He organized the Observation Department for Nervous and Mental Diseases at the City Hospital of Cleveland, and also at Lakeside Hospital.

Dr. Stone was interested always in military affairs. As a member of the National Guard of Ohio, he saw duty with the 112th Engineers during the Dayton Flood and with the same organization Dr. Stone served on the Mexican border and later saw service with the 37th Division, Ohio N. T., in France, from which organization he was drafted for special service in the Neuro-Psychiatric Department of the American Expeditionary Forces, under the late Col. Thomas W. Salmon.

Throughout his extremely active life Dr. Stone interested himself in the furtherance of the aims and ideals of organized medicine. Locally, he was active in the Academy of Medicine of Cleveland and was President of that organization in 1926. He served the Ohio State Medical Association in many important committee assignments, as member of the House of Delegates and later as President. To the American Medical Association he served as member of the House of Delegates for many years. His service has further been freely given to the Cleveland Medical Library Association from the years 1929 through 1938.

Dr. Stone was a member of all his local medical organizations, in addi-

tion to which he has been a Fellow of the American College of Physicians since 1920, and a life member of the College since 1937. He was a member of the American Psychiatric Association and of many local medical and fraternal organizations.

An intense worker, a strong supporter of the aims of organized medicine, an inspiring teacher, a deep student, a kindly gentleman, beloved by his friends and by his patients, his memory is cherished and his loss condoned by friends, colleagues, and patients alike. His life was one of complete service. He never swerved from the duties of public or private service, no matter how difficult the task.

RICHARD DEXTER, M.D., F.A.C.P.
Cleveland, Ohio

DR. ORAN IDNIRE CUTLER

Dr. Oran Idnire Cutler (Associate) died September 15, 1939, at 39 years of age. His untimely death was the result of an automobile accident which occurred as he was returning from a meeting of the Los Angeles Pathological Society.

He was born December 25, 1899, at Swedesburg, Iowa. He received his B.S. degree from Union College (Nebraska) and his M.D. degree from the College of Medical Evangelists in 1924. His intern year was served at the Santa Tomas Hospital, Panama, Canal Zone. He was awarded a fellowship in Pathology by the National Research Council and served one year, 1926–27, under Dr. William Ophüls at Stanford University, and a second year under Dr. H. Gideon Wells at the University of Chicago; he returned to Chicago to serve as instructor in Dr. Wells' department during the summer of 1932. With the exception of this period at Chicago, he served continuously in the Pathology Department of his Alma Mater, the College of Medical Evangelists, Loma Linda and Los Angeles, California, from 1928 to the time of his death, as Instructor, Assistant Professor, Associate Professor, and Professor of Pathology. He was a member of the American Association of Pathologists and Bacteriologists, the American Society of Clinical Pathologists, and the Los Angeles Pathological Society, as well as his county and state medical societies and the American Medical Association. He was a continuous participant in the activities of these various societies. He served as pathologist to the Los Angeles County Hospital, the San Bernardino County Hospital, and the Riverside County Hospital, also as Coronor's Physician in San Bernardino County.

His loss is keenly felt by all who have been associated with him in these activities. His scientific interest and integrity were of the highest order and all who came in contact with him felt his stimulus. His prime activities were those of his pathology teaching. As a teacher, he had few peers. His passing has been an irreparable loss to his students, his medical school, his

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teaching and professional fellows, and to all who learned to trust him and depend upon him.

NEWTON EVANS, M.D., F.A.C.P.,
Los Angeles, Calif.

DR. WILLIAM BURR SOPER

Dr. William Burr Soper, medical director of the William Wirt Winchester Hospital, tuberculosis unit of the New Haven Hospital, and associate professor of medicine in the Yale University School of Medicine, died in New Haven Hospital on October 30, 1939 of brain tumor.

Dr. Soper was born at Bloomington, Ill., Dec. 28, 1882. He was graduated from Yale University in 1904, and received his medical degree from Columbia University College of Physicians and Surgeons in 1908. While an undergraduate at Yale he was secretary of the Freshman Navy, and played on the varsity football team. He was also a member of the banjo and mandolin club, Psi Upsilon, and Skull and Bones.

After receiving his medical degree Dr. Soper was an intern, 1909–11, at Presbyterian Hospital, New York City, and Bacteriologist and Serologist, 1911–13. In 1913–14 he took postgraduate work in pathology at the University of Freiburg, Germany. In 1914 he became engaged in tuberculosis work at Saranac Lake, N. Y. He remained there until 1917 when he was commissioned Captain in the United States Medical Corps, being assigned to Base Hospital No. 2, the Presbyterian Hospital Unit from New York that went overseas immediately after being organized. The unit was assigned to the British Expeditionary forces, taking over a hospital in Etretet, France. Dr. Soper was made Commanding Officer of the Unit in 1918, and in the same year was promoted to rank of Major.

Upon his return to the United States in 1919 he joined the Rockefeller Foundation, engaged in work for the prevention of tuberculosis in France. At the close of this work in September, 1921, he returned to Saranac Lake where he remained until appointed the first director of the Bureau of Tuberculosis of the New Haven Department of Health in 1926. The following year, after the William Wirt Winchester Hospital was restored to civilian use, Dr. Soper became its medical director, in which position he was serving at the time of his death. Coincident with this appointment he became a member of the faculty of the Yale University School of Medicine in which he held the rank of associate professor of medicine. In addition to his teaching work he served as tuberculosis consultant in the Yale Department of University Health. In 1937 Dr. Soper was appointed to the New Haven Board of Health Commissioners and he served on the medical advisory committee of the Visiting Nurse Association since 1933.

Dr. Soper was a Diplomate, American Board of Internal Medicine, member of his county and state medical societies, American Clinical and Clima-

tological Association and Interurban Clinical Club; member and former Vice President of the National Tuberculosis Association; Fellow, American Medical Association; Fellow of the American College of Physicians since 1933. He was the author of numerous medical articles including translations of scientific papers from the French, and was frequently called upon to deliver lectures on tuberculosis.

From the above it can be seen that Dr. Soper was a busy and hardworking student keenly interested in the welfare of his fellow man. His friendly and delightful personality endeared him to all with whom he came in contact, and his untimely death is mourned by his medical associates, and by hosts of others to whom he was not only physician but friend as well.

CHARLES H. TURKINGTON, M.D., F.A.C.P.,
Governor for Connecticut

DR. ROY GEORGE PFOTZER

The death of Dr. Roy George Pfotzer occurred suddenly on August 9, 1939.

Dr. Pfotzer was born in Buffalo on November 20, 1892; attended University of Buffalo, earning a degree in Chemistry; M.D., C.M., 1924 and D.P.H., 1924, Queens University, Faculty of Medicine; Intern, Buffalo City Hospital, 1924–25; Assistant Attending Physician, 1925–27, Attending Physician, 1927–30, and Associate Visiting Physician, Buffalo City Hospital; formerly Assistant Attending Physician and more recently Electrocardiographer and Attending Physician, Millard Fillmore Hospital; Associate in Medicine, University of Buffalo School of Medicine; at one time, Biochemist in the Department Laboratory of the City of Buffalo; First Lieutenant, Sanitary Corps, U. S. Army and assigned to Red Cross Work in Serbia as Sanitary Officer during the World War; Member, Academy of Medicine of Buffalo, Erie County Medical Society, New York State Medical Association, American Heart Association, Association for the Study of Internal Secretions, American Medical Association and Fellow of the American College of Physicians since 1934; Diplomate, American Board of Internal Medicine.

Dr. Pfotzer practiced Internal Medicine in Buffalo and taught in the Medical School most of the time. He was very active as Attending Physician at the Millard Fillmore Hospital.

Dr. Pfotzer's work was of the highest type and he was an excellent teacher, with a most exceptional foundation. He was quite active in the medical life of Buffalo and his loss is deeply regretted by the whole community.

NELSON G. RUSSELL, M.D., F.A.C.P.,
Governor for Western New York

DR. ARTHUR BURKE O'BRIEN

Dr. Arthur Burke O'Brien (Associate) died at Rochester, N. Y., July 6, 1939, as a result of an automobile accident. He was born at Ellicottville, N. Y., January 24, 1896. After doing his pre-medical work at Niagara University he entered the University of Buffalo School of Medicine from which he graduated in 1921. He interned at St. Mary's Hospital, 1921–22, and then engaged in the practice of general medicine in Rochester. He was appointed to the medical staff of St. Mary's Hospital in 1923 and was advanced to Senior Medical Attendant in 1928, the latter appointment held until his death.

Dr. O'Brien was a member of the Rochester Academy of Medicine, Rochester Pathological Society, Monroe County Medical Association and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1939.

DAVID B. JEWETT, M.D., F.A.C.P.

PROGRAM
TWENTY-FOURTH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
CLEVELAND, OHIO

April 1–5, 1940

GENERAL SESSIONS AND LECTURES

O. H. Perry Pepper, President

CLEVELAND COMMITTEE ON ARRANGEMENTS

Howard T. Karsner, General Chairman

Edward H. Cushing
Harold Feil
Joseph M. Hayman, Jr.
E. P. McNamee
V. C. Rowland
John A. Toomey

COMMITTEE ON CLINICS AND DEMONSTRATIONS

Joseph M. Hayman, Jr., Chairman

Samuel S. Berger
Russell L. Haden
Fred C. Oldenburg
Harry V. Paryzek
Robert M. Stecher
Charles T. Way
Harley A. Williams

COMMITTEE ON TRANSPORTATION

Edward H. Cushing, Chairman

McKinley London
J. C. Placak

COMMITTEE ON ENTERTAINMENT

E. P. McNamee, Chairman

F. A. LeFevre
H. D. Piercy
J. P. Tucker

COMMITTEE ON AUDITORIUM

John A. Toomey, Chairman

C. L. Hartsock
A. D. Nichol
R. A. Reading

COMMITTEE ON PUBLICITY

V. C. Rowland, Chairman
H. van Y. Caldwell, Vice-chairman

Everett N. Collins
Hubert C. King
M. W. Martin
S. J. Wolpaw

COMMITTEE ON PANEL DISCUSSIONS

Harold Feil, Chairman

Frank J. Doran
A. C. Ernstene
Charles S. Higley
Roy W. Scott
Carl J. Wiggers

WOMEN'S ENTERTAINMENT COMMITTEE

Mrs. Harley A. Williams, Chairman
Mrs. Harold Feil, Vice-chairman
Mrs. Howard T. Karsner, Vice-chairman

Mrs. William P. Garver
Mrs. Russell L. Haden
Mrs. William R. Hallaran
Mrs. Charles L. Hartsock
Mrs. Joseph M. Hayman, Jr.
Mrs. Charles L. Higley
Mrs. Edgar P. McNamee
Mrs. Fred C. Oldenburg
Mrs. V. C. Rowland
Mrs. Robert M. Stecher
Mrs. Carl J. Wiggers

WELCOME TO CLEVELAND

A cordial welcome is extended to the Fellows and Associates of the American College of Physicians and their guests by the medical profession of the entire community, together with the Academy of Medicine of Cleveland, the Faculty of Medicine of Western Reserve University, and the members of the staffs of the various hospitals in the city. Cleveland prides itself upon the spirit of its hospitality to all visitors and this will be particularly true as concerns so distinguished an organization as the American College of Physicians. All hospitals, whether participating in the programs or not, will be glad to receive visitors who wish to study physical equipment, organization, and services of various kinds. Western Reserve University will welcome visitors to the School of Medicine and the associated hospitals, as well as to the various related professional schools.

As will be seen by reference to the program, certain hospitals and members of their staffs will actively participate in the Clinics. In addition, many of the Clinics will be conducted in part by distinguished visitors. The endeavor has been to provide a diversified and well rounded program of interest and benefit to all the members of the College. For this year at least, the usual Round Tables will be replaced by Panel Discussions. By this means, it is hoped that there will be informality and intimacy in the conferences, between those who conduct the panels and those who attend them. Each Panel is so arranged as to provide coverage of the special fields within the scope of each particular Panel. For that reason, each Panel will have from two to five distinguished physicians as leaders. The freedom of contact with these outstanding leaders should provide much in the way of information and inspiration.

The various public and private institutions of the city are deeply interested in welcoming to their halls the members of the College and their guests. In all of these, the registration badge will be sufficient for admission. The Cleveland Museum of Art represents more than a collection of objects. It is an institution which has a widespread influence in the community through lectures, demonstrations, and other activities of the modern museum. The exhibits are varied and of great interest, including art of the classical period as well as that of modern times. The Cleveland Museum of Natural History, although only recently established, has a collection now well known throughout the world. The history of the Western Reserve is characteristic of the spread of culture in the new world. The Western Reserve Historical Society occupies two buildings, one at University Circle and one on East Boulevard. The former houses a library of over 200,000 volumes, files of newspapers and an extensive genealogical file. The latter contains many objects of historical interest, including extensive Washingtoniana and the largest collection of material on Napoleon in this country. The Dunham Tavern, dating from the early nineteenth century, is open from 1 to 5 each afternoon except Monday, and contains much in the way of design, furniture and the like, to delight the hearts of those

interested in early Americana. The Garden Center, at University Circle, is open daily, except Monday, and also on Tuesday evening. An extensive horticultural library and exhibits are available, and a graduate of the Cambridge School of Landscape Architecture is in attendance.

The Cleveland Medical Library Association building is on Euclid Avenue near the University Hospitals. Beautifully designed and equipped, it houses more than 54,000 volumes and contains exhibits of great interest to the medical historian. It is open from 9:00 a.m. to 10:00 p.m. on Monday, Wednesday and Friday, and from 9:00 a.m. to 6:00 p.m. on Tuesday, Thursday and Saturday.

Information as to numerous other places well worthy of a visit will be available at the Registration Bureau.

GENERAL INFORMATION

Cleveland Headquarters

Public Auditorium—General Headquarters
Hotel Statler—Hotel Headquarters

The Cleveland Public Auditorium will be general headquarters for registration, exhibits, general sessions, panel discussions and special lectures.

The Hotel Statler will be headquarters for Officers, Regents, Governors and members of the College; also headquarters for the Women's Entertainment Committe, the President's Reception and the Annual Banquet.

List of Cleveland Hotels	Blocks from Auditorium	Rates per day*	
		Single Room	Double Room
HOTEL STATLER	4	$3.00–6.00	$4.50–8.00
Allerton Hotel	5	2.50–2.75	4.00–4.50
Auditorium Hotel	¼	2.00–2.50	3.50–6.00
Carter Hotel	4	3.00–5.00	4.50–8.00
Cleveland Hotel	3	3.00–5.00	4.50–8.00
Hollenden Hotel	1½	3.00–5.00	4.50–8.00

* All rooms with private bath.

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1940 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Members of the Academy of Medicine of Cleveland, without registration fee, upon presentation of their 1940 membership cards.

(*d*) Medical students (third and fourth years only) pursuing courses at Western Reserve University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at this institution; exhibits, morning lectures, panel discussions and general sessions.

(*e*) House Officers of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, panel discussions and general sessions.

(*f*) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open at the Public Auditorium on Sunday, March 31, from 2:30 to 5:00 in the afternoon, and 7:00 to 9:00 in the evening. The permanent Registration Bureau at the Auditorium will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, April 1–5.

REGISTRATION BLANKS FOR ALL CLINICS, DEMONSTRATIONS AND PANEL DISCUSSIONS will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Public Auditorium, and in the lobby of the Hotel Statler.

TRANSPORTATION—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Physicians should consult their local ticket agents.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting.

Special Taxicab Rates—The following rates will apply for all Yellow Cabs upon presentation of the Registration Badge to the driver, and include one to four passengers:

From any down town hotel to Lakeside Hospital, St. Luke's Hospital or Mt. Sinai Hospital	$1.00
From any down town hotel to Charity Hospital	.35
From any down town hotel to St. Alexis Hospital, the Cleveland Clinic or City Hospital	.75
To or from any down town hotels and the Municipal Auditorium	.25

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4:45 p.m., Thursday, April 4, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. James D. Bruce, Ann Arbor, Mich.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled, as indicated. Special meetings will be announced and posted.

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Statler, Sunday evening, March 31, at seven o'clock.

COMMITTEE ON CREDENTIALS

Sunday, March 31, 9:00 a.m. . . . . Public Auditorium, Executive Secretary's Office

BOARD OF REGENTS

Public Auditorium

Sunday, March 31, 2:30 p.m.
Tuesday, April 2, 12:00 m.*
Friday, April 5, 12:00 m.*

BOARD OF GOVERNORS

Public Auditorium

Monday, April 1, 5:00 p.m.
Wednesday, April 3, 12:00 m.*

SPECIAL FEATURES

Monday, April 1, 1940

THE ANNUAL SMOKER will be held in the Ballroom of the Hotel Statler at 10:20 p.m., immediately following the evening meeting. The program, largely in the nature of variety and vaudeville, will be given by professionals. Light refreshments and beer will be served. Admission will be limited to those who display the official registration badge. Fellows and Associates, local and visiting physicians and the technical exhibitors are invited to attend the Smoker as guests of the College. Men only.

Wednesday, April 3, 1940

CONVOCATION OF THE COLLEGE—8:30 p.m., Music Hall, Public Auditorium. All Masters and Fellows of the College, and those to be received into Fellowship, should be present. Newly elected Fellows who have not yet been received into Fellowship are requested to assemble (room to be announced later) at 7:45 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Music Hall, to which they will be conducted by the Convocation Marshal promptly at 8:30 o'clock. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation program will include an address by the President of the College, the presentation of newly elected Fellows by the Secretary General, conferring of Fellowships, award of the John Phillips Memorial Medal, announcement of the Research Fellowships awarded for 1940 by the College, and the presentation of the Annual Convocation Address by Charles F. Martin, M.D., M.A.C.P., Emeritus Dean and Emeritus Professor of Medicine, McGill University Faculty of Medicine, President of the Canadian Society of Occupational Therapy, and President of the Art Association of Montreal, Montreal, Canada. It is particularly appropriate for Dr. Martin to address the College on the occasion of its Convocation. He is the only remaining Master of the College and he was the President of the College, 1928–29, during the period of reorganization and shaping of new policies and destinies of the organization.

The Presidential Reception, with dancing, will follow in the Ballroom of the Hotel Statler one-half hour after the termination of the exercises. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception at the Hotel Statler.

Thursday, April 4, 1940

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Ballroom of the Hotel Statler at eight o'clock, Thursday evening. Dr. Howard T. Karsner, General Chairman of the Twenty-fourth Annual Session of the College, will be the Toastmaster. The address of the evening will be given by Mr. Grove Patterson, Editor of the Toledo Blade. Mr. Patterson is well known as an interesting and entertaining speaker. His address is entitled, "Peeps at the Presidents," referring, of course, to the Presidents of the United States.

* Buffet luncheon served.

All members of the College, physicians of Cleveland and visitors attending the Session, with their families and friends, are cordially invited. Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, $4.00.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the Women's Entertainment Committee will be located in the Pine Room, mezzanine floor, Hotel Statler. Each visitor will receive a program of the activities planned for her entertainment by the Committee. A secretary will be in charge to assist visitors in arranging their program. Visiting women are requested to register *immediately* after arrival. Information concerning theaters, restaurants and places of entertainment will be available at the registration desk.

Members of the Committee will be at the place of registration and will wish to do everything in their power to make the visit to Cleveland pleasant and memorable. Inasmuch as the places available for certain of the events are limited, it is urgently requested that each Fellow or Associate, who will be accompanied by ladies, return the card accompanying the program, as promptly as possible. It is necessary for the Committee to conclude its arrangements in advance of the time of meeting.

Upon registration, the ladies are requested to confirm any reservations they have made and to make such additional reservations as they wish.

Monday, April 1, 1940

Morning: Registration, Hotel Statler.

Afternoon: 4:00 to 5:30 o'clock. Complimentary tea at the Women's City Club, Bulkley Building, Euclid Avenue, two blocks east of Hotel Statler.

Tuesday, April 2, 1940

Afternoon: 12:30 p.m. Luncheon and Style Show, The Higbee Company, Public Square, nine short blocks from Hotel Statler. $1.25 per person.

Wednesday, April 3, 1940

Noon: "Brunch" at Wade Park Manor, followed by Playlet, "Mr. Godey Presents." Tickets; $1.50. Wade Park Manor is about four miles from Hotel Statler and can be reached by street car or taxicab.

Nearby are the Cleveland Museum of Art and the Garden Center. Registration badges admit to both, and visitors are welcome.

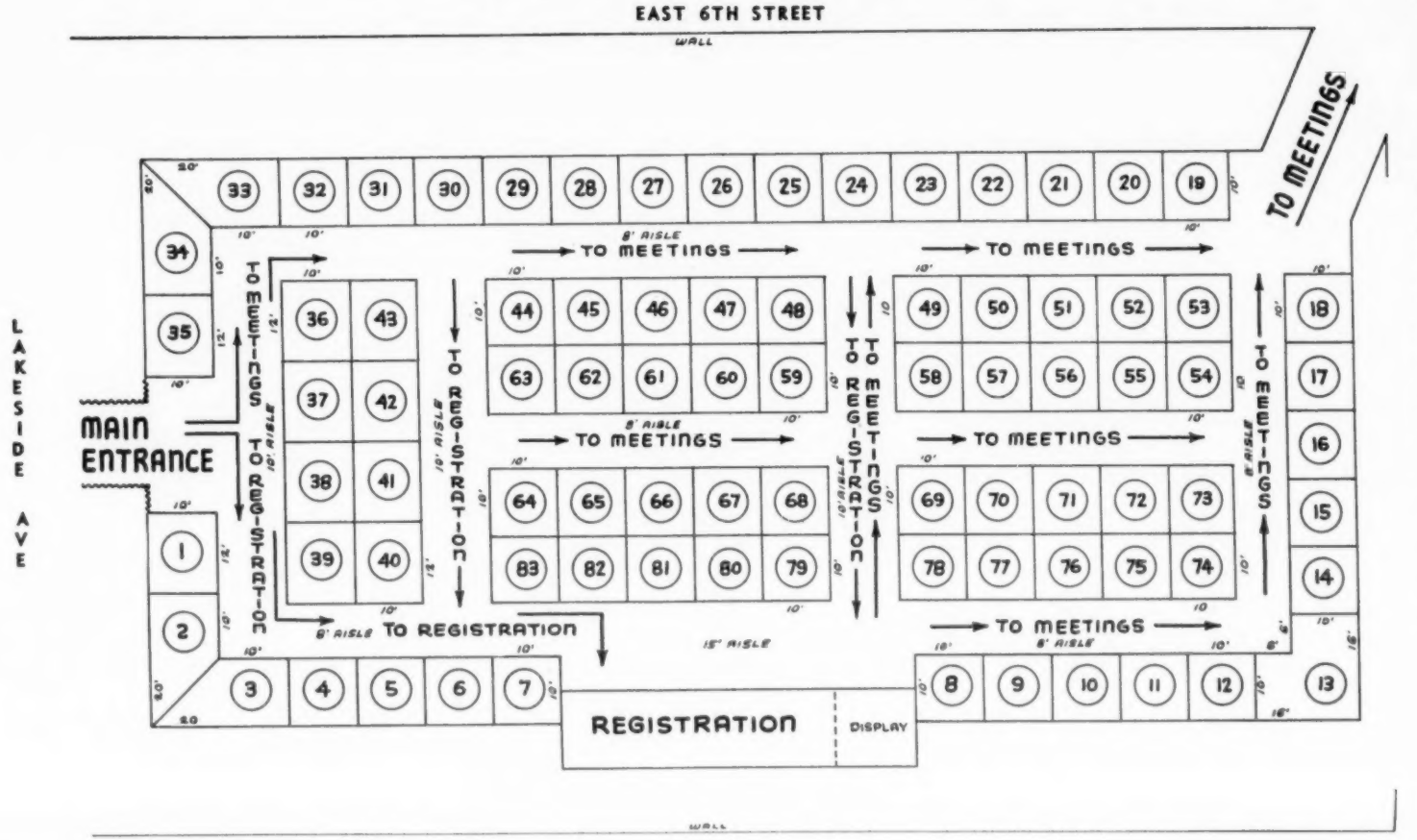
Evening: 8:30 p.m. Convocation in Music Hall of Public Auditorium, followed by President's Reception in Ballroom of Hotel Statler.

Thursday, April 4, 1940

Afternoon: 3:00 to 5:00 o'clock. Complimentary tea at Cleveland Skating Club, 2106 East 130th Street, and amateur exhibition of figure skating. Transportation by taxicab will be provided. Limited to 200 guests.

Evening: 8:00 p.m. Annual Banquet of the College, Ballroom, Hotel Statler.

FLOOR PLAN OF THE TECHNICAL EXHIBIT



SPECIAL FEATURES

(Concluded)

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the main floor of the Cleveland Public Auditorium.

By official action of the Board of Regents of the College, the technical exhibits have been raised to a higher level of excellence through the elimination of all irrelevant and non-scientific entries. The rules adopted governing this Exhibit are as follows:

(1) Exhibitors shall be admitted on invitation only;
(2) The initial approved "Invitation List" shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved. Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books;
(3) Additions to the initial approved "Invitation List" may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization;
(4) The "Invitation List" may be revised annually on the recommendation of the Committee.

The Committee on Exhibits has approved each exhibit before extending invitations. Members and visiting physicians will find these exhibits more interesting and more beneficial than the usual "commercial exhibit." The exhibits have been selected because they are particularly representative of the interests of Internal Medicine and its allied specialties. Here conveniently assembled will be the leading medical books, pharmaceuticals, apparatus and appliances, specialized physicians' furniture and other products, making up much of the important armamentarium of medical practice. Each doctor should take advantage of this opportunity to inspect the latest developments in these lines, not only for the educational and practical value they offer, but also to demonstrate their interest in and courtesy toward these allies of the medical profession and of the College. These exhibitors and their displays merit some special attention on the part of our members because they make a large contribution, educational as well as financial, to the Annual Sessions of the College. Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

LIST OF EXHIBITORS

(Not yet complete)

	Space
Jones Metabolism Equipment Company, Chicago, Ill.	1
The G. F. Harvey Company, Saratoga Springs, N. Y.	2
The Williams & Wilkins Company, Baltimore, Md.	3
Frober-Faybor Co., Cleveland, Ohio	4
Hille Laboratories, Chicago, Ill.	5
John Wyeth & Bro., Inc., Philadelphia, Pa.	6
W. B. Saunders Company, Philadelphia, Pa.	7
Kalak Water Co. of New York, Inc., New York, N. Y.	8
Davies, Rose & Co., Ltd., Boston, Mass.	9
Cameron Surgical Specialty Co., Chicago, Ill.	10
Parker, White & Heyl, Inc., Danbury, Conn.	11
American Hospital Supply Corporation. Chicago, Ill.	12

Cambridge Instrument Co., Inc., New York, N. Y. 13
Ralston Purina Company, Inc., St. Louis, Mo. 14
Mallinckrodt Chemical Works, St. Louis. Mo. 15
The Macmillan Company, New York, N. Y. 18
Paul B. Hoeber, Inc., New York, N. Y. 19
Devereux Schools, Inc., Berwyn, Pa. 20
Becton, Dickinson & Co., Rutherford, N. J. 21–22
The Cream of Wheat Corporation, Minneapolis, Minn. 23
Merck & Co. Inc., Rahway, N. J. 24–25
W. F. Prior Company, Inc., Hagerstown, Md. 26
Ayerst, McKenna & Harrison (U. S.) Limited, Montreal, Que., Canada 27
Cameron Surgical Specialty Co., New York, N. Y. 28
Schering Corporation, Bloomfield, N. J. 29
The C. V. Mosby Company, St. Louis, Mo. 30
The Arlington Chemical Company, Yonkers, N. Y. 31
Medical Case History Bureau, New York, N. Y. 32
Warren E. Collins, Inc., Boston, Mass. 33
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y. 34
Frederick Stearns & Company, Detroit, Mich. 35
J. B. Lippincott Company, Philadelphia, Pa. 36
Lederle Laboratories, Inc., New York, N. Y. 37–38–39
General Electric X-Ray Corporation, Chicago, Ill. 40–41
Eli Lilly & Company, Indianapolis, Ind. 42–43
LaMotte Chemical Products Company, Baltimore, Md. 44
Smith, Kline & French Laboratories, Philadelphia, Pa. 45–46
Gerber Products Company, Fremont, Mich. 47
Oxford University Press, New York, N. Y. 48
Vegex, Incorporated, New York, N. Y. 49
E. R. Squibb & Sons, New York, N. Y. 50–51
The Muller Laboratories, Baltimore, Md. 52
Sanborn Company, Cambridge, Mass. 53
Winthrop Chemical Company, Inc., New York, N. Y. 54–55
The Maltine Company, New York, N. Y. 56
Riedel-de Haen, Inc., New York, N. Y. 57
Petrolagar Laboratories, Inc., Chicago, Ill. 58
Bilhuber-Knoll Corp., Orange, N. J. 59
Charles B. Knox Gelatine Co., Inc., Johnstown, N. Y. 60
Lea & Febiger, Philadelphia, Pa. 63
Ciba Pharmaceutical Products, Inc., Summit, N. J. 64–65
Kellogg Company, Battle Creek, Mich. 66
F. A. Davis Company, Philadelphia, Pa. 67
S. M. A. Corporation, Chicago, Ill. 68
D. Appleton-Century Co., Inc., New York, N. Y. 69
H. J. Heinz Company, Pittsburgh, Pa. 70
Doak Company, Incorporated, Cleveland, Ohio 72
Parke, Davis & Company, Detroit, Mich. 73
Mead Johnson & Company, Evansville, Ind. 74–75
The Wm. S. Merrell Company, Cincinnati, Ohio 76
Thomas Nelson & Sons, New York, N. Y. 77
Scientific Sugars Co., Columbus, Ind. 78
Picker X-Ray Corporation, New York, N. Y. 79
Gradwohl Laboratories, St. Louis, Mo. 80
The Medical Bureau, Chicago, Ill. 81
Laboratory Nativelle, New York, N. Y. 82
The E. L. Patch Company, Boston, Mass. 83

OUTLINE OF CLEVELAND SESSION

Municipal Auditorium events are indicated in **bold type**

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
	April 1	April 2		April 3		April 4		April 5	
9:00 a.m. to 12:00 m.	Morning free **Registration, Exhibits, etc.**	Hospital Clinics	**Morning Lectures (10:00–12:00)**	Hospital Clinics	**Morning Lectures (10:00–12:00)**	Hospital Clinics	**Morning Lectures (10:00–12:00)**	Hospital Clinics	**Morning Lectures (10:00–12:00)**
12:00 m. to 1:00 p.m.	Luncheon	Luncheon		Luncheon		Luncheon		Luncheon	
1:00 p.m. to 2:00 p.m.		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**	
2:00 p.m. to 5:30 p.m.	**1st General Session**	**3d General Session**		**4th General Session**		**5th General Session** **Annual Business Meeting**		**6th General Session**	
5:30 p.m. to 8:00 p.m.	Dinner	Dinner		Dinner		ANNUAL BANQUET			
8:00 p.m. to 11:00 p.m.	**2d General Session** followed by SMOKER			**CONVOCATION,** followed by President's Reception					

GENERAL SESSIONS

The program of the General Sessions offers as usual a wide variety of subjects, each chosen because of its current interest and importance. In every instance, the speaker has a personal interest in his subject and can be counted upon to present new and important material. The College is fortunate in having a high percentage of the speakers from its own membership and in welcoming new guests to its program.

With the coöperation of the Surgeons General of the Army and Navy, one session has been arranged to present various matters of military interest to all in view of present-day conditions. Included are papers on aviation and submarine medical problems.

Among the newer topics to be presented are the relation of the endocrines to edema formation; the occurrence of vitamin deficiencies in gastrointestinal conditions and the very suggestive new work on the use of agents obtained from soil microörganisms in the treatment of experimental infections. Treatment is well represented by papers on the surgical therapy of hypertension; a report on the newest drug of the sulfapyridine type, also on one of the newer respiratory stimulants. In the final session four papers on psychosomatic medicine are grouped together to form an authoritative symposium.

The mention of these few papers neglects the many other equally important papers in other fields of medicine.

GENERAL SESSIONS PROGRAM

Cleveland Public Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 1, 1940

Presiding Officer

Howard T. Karsner, F.A.C.P., Cleveland, Ohio

p.m.

2:30 Addresses of Welcome:

HOWARD T. KARSNER, F.A.C.P., General Chairman, Twenty-fourth Annual Session; Professor of Pathology and Director of Institute of Pathology, Western Reserve University.

HON. HAROLD H. BURTON, Mayor of the City of Cleveland.

WINFRED G. LEUTNER, President of Western Reserve University.

PARKE G. SMITH, President of the Ohio State Medical Society.

RUSSELL L. HADEN, F.A.C.P., President, The Academy of Medicine of Cleveland.

TORALD SOLLMANN, F.A.C.P., Dean, School of Medicine, Western Reserve University.

Response to Addresses of Welcome:

O. H. PERRY PEPPER, F.A.C.P., President, American College of Physicians; Professor of Medicine, University of Pennsylvania.

3:45 INTERMISSION.

4:00 Specialization in General Medicine.

WILLIAM B. BREED, F.A.C.P., Associate in Medicine, Harvard University Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

4:20 Postgraduate Education.
HUGH J. MORGAN, F.A.C.P., Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

4:40 The First Four Years of the American Board of Internal Medicine and Its Apparent Influence on Medical Education and Practice.
ERNEST E. IRONS, F.A.C.P., Clinical Professor of Medicine and Chairman of Department, Rush Medical College; Chairman, American Board of Internal Medicine; Chicago, Ill.

5:00 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, April 1, 1940

Presiding Officer

James D. Bruce, F.A.C.P., Ann Arbor, Mich.

SYMPOSIUM ON MILITARY MEDICINE

p.m.

8:00 Medical Problems Encountered in Military Service.
COL. CHARLES C. HILLMAN, M.C., U.S.A. (F.A.C.P.).

8:20 Epidemiology in the Army.
LT. COL. JAMES S. SIMMONS, M.C., U.S.A. (F.A.C.P.).

8:40 Organization and Administration of the Medical Department.
LT. COL. CHARLES B. SPRUIT, M.C., U.S.A. (By invitation.)

9:00 Developments in Aviation Medicine.
CAPT. HARRY G. ARMSTRONG, M.C., U.S.A. (Associate, A.C.P.).

9:20 Tetanus Toxoid Immunization in the U. S. Navy.
COMDR. W. W. HALL, M.C., U.S.N. (F.A.C.P.).

9:40 Physiological Effects of Increased Barometric Pressure; Application of Findings to Clinical Medicine.
LT. ALBERT R. BEHNKE, M.C., U.S.N. (By invitation.)

10:00 ADJOURNMENT.

10:20 o'Clock

SMOKER

Ballroom, Hotel Statler

A diverting and amusing program has been arranged. Admission by registration badge. Men only.

THIRD GENERAL SESSION

Tuesday Afternoon, April 2, 1940

Presiding Officer

J. Morrison Hutcheson, F.A.C.P., Richmond, Va.

p.m.

2:00 Results of Treatment of Essential Hypertension: Medical versus Surgical.
E. V. ALLEN, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Chief of Section in Division of Medicine, Mayo Clinic; Rochester, Minn., and

A. W. Adson (by invitation), Professor of Neurosurgery, University of Minnesota (Mayo Foundation); Chief of Department of Neurosurgery, Mayo Clinic; Rochester, Minn.

2:30 Prevention of Pernicious Anemia—Recognition of the Latent Stage in Relatives.

John M. Askey, F.A.C.P., Assistant Professor of Clinical Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

2:45 Endocrine Abnormalities in Puberty.

Joseph C. Aub (by invitation), Associate Professor of Medicine, Harvard University Medical School, Boston, Mass., and

Ira Nathanson (by invitation), Boston, Mass.

3:15 A Study of the Acute Leukoses.

Joseph Kaufmann, F.A.C.P., Assistant Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Canada, and

Louis Lowenstein (by invitation), Montreal, Que., Canada.

3:35 INTERMISSION.

4:00 Pancreatitis: An Analysis of Types and Causes.

Kenneth M. Lynch, F.A.C.P., Professor of Pathology and Vice Dean, Medical College of the State of South Carolina, Charleston, S. C.

4:15 Changes in the Human Heart During Growth and Hypertrophy.

Joseph T. Wearn, F.A.C.P., Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

4:35 Pathogenesis of Banti's Disease.

William P. Thompson (Associate, A.C.P.), Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

5:00 ADJOURNMENT.

FOURTH GENERAL SESSION

Wednesday Afternoon, April 3, 1940

Presiding Officer

Allen A. Jones, F.A.C.P., Buffalo, N. Y.

p.m.

2:00 Hematological Aspects of Space Consuming Lesions of the Bone Marrow.

Stacy R. Mettier, F.A.C.P., Associate Professor of Medicine, University of California Medical School, San Francisco, Calif.

2:15 The Comparative Effectiveness of Sulfathiazol and Sulfapyridine in Pneumococcic Pneumonia.

H. F. Flippin (Associate, A.C.P.), Instructor in Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, Pa., and

Leon Schwartz (by invitation), Assistant Instructor in Medicine, University of Pennsylvania, Philadelphia, Pa.

2:30 The Treatment of Ulcerative Colitis with Sulfanilamide.

E. N. Collins, F.A.C.P., Head, Section on Gastrointestinal Diseases, Cleveland Clinic, Cleveland, Ohio.

2:50 Concerning the Correlation of the Pathology and Symptoms of Coronary Artery Disease.
FRED M. SMITH, F.A.C.P., Professor and Head of Department of Theory and Practice of Medicine, State University of Iowa College of Medicine; Editor-in-Chief, American Heart Journal; Iowa City, Iowa.

3:10 Malarial Coma.
CONLEY H. SANFORD, F.A.C.P., Professor of Medicine and Chief of Division of Medicine, University of Tennessee College of Medicine, Memphis, Tenn.;
P. T. CRAWFORD (Associate, A.C.P.), Memphis, Tenn., and
OTIS S. WARR, JR. (by invitation), Memphis, Tenn.

3:30 INTERMISSION.

4:00 Rôle of Pituitary in Edema of Nephritis.
FRANK H. ROBINSON* (Associate, A.C.P.), Jamestown, N. Y., and
LEE E. FARR (by invitation), Associate in Medicine, The Rockefeller Institute for Medical Research, New York, N. Y.

4:20 The Rôle of the Gonadal and Adrenal Cortical Hormones in the Production of Edema.
GEORGE W. THORN, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

4:40 The Relation of Listerella to Human Infection.
LOUIS A. JULIANELLE (by invitation), Associate Professor of Applied Bacteriology and Immunology, Washington University School of Medicine, St. Louis, Mo.

5:00 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 3, 1940

8:30 o'Clock

Music Hall, Public Auditorium

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. The President's Address.
   O. H. Perry Pepper.
2. Presentation of Newly-Elected Fellows and Recital of the Pledge.
   George Morris Piersol, Secretary-General.
3. Presentation of John Phillips Memorial Medal for 1939–40.
4. Announcement of Research Fellows of the College for 1940.
5. Convocational Address:
   CHARLES F. MARTIN, M.A.C.P., Emeritus Dean and Emeritus Professor of Medicine, McGill University Faculty of Medicine; President, Alexandra Hospital; President, Canadian Society of Occupational Therapy; President, Art Association of Montreal, Montreal, Que., Canada.

* Deceased since program assignment.

President's Reception

The Reception and Dance will follow one-half hour after the completion of this program, and will be held in the Ballroom of the Hotel Statler. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception at the Hotel Statler.

FIFTH GENERAL SESSION

Thursday Afternoon, April 4, 1940

Presiding Officer

Charles H. Cooke, F.A.C.P., Asheville, N. C.

p.m.

2:00 Industrial Medicine as a Specialty and Its Relation to General Practice.
GEORGE H. GEHRMANN, F.A.C.P., Medical Director, E. I. duPont de Nemours and Company, Wilmington, Del.

2:20 The Effect of Specific Agents Extracted from Soil Microörganisms upon Experimental Bacterial Infections.
RENÉ J. DUBOS (by invitation), Associate Member, Rockefeller Institute for Medical Research, New York, N. Y.

2:50 Vitamin Deficiencies and Gastrointestinal Disease.
THOMAS T. MACKIE, F.A.C.P., Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

3:10 Vitamins and Peptic Ulcer.
HENRY FIELD, JR. (by invitation), Associate Professor of Internal Medicine, University of Michigan, Ann Arbor, Mich.;
WILLIAM D. ROBINSON (by invitation), Ann Arbor, Mich.; and
DANIEL MELNICK (by invitation), Ann Arbor, Mich.

3:30 INTERMISSION.

4:00 The Importance of Allowing Time for "Physiological Adjustment" in Establishing the Diet in Diabetes.
R. R. SNOWDEN, F.A.C.P., Associate Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

4:15 The Clinical Significance of Iron in the Blood.
REGINALD FITZ, F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine, Boston, Mass.

4:30 Observations upon the Effect of Coramine in Certain Cardiac States.
WILLIAM D. STROUD, F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., and
PAUL H. TWADDLE (by invitation), Morris W. Stroud, Jr. Fellow in Cardiology, Pennsylvania Hospital, Philadelphia, Pa.

4:45 ADJOURNMENT, to be followed by

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports will be made by the Treasurer and the Executive Secretary; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. James D. Bruce, Ann Arbor, Mich., will be inducted into office.

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8:00 o'Clock

Ballroom, Hotel Statler

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: Howard T. Karsner, F.A.C.P., Cleveland, Ohio.
Address: "Peeps at the Presidents."
Mr. Grove Patterson, Editor, Toledo Blade, Toledo, Ohio.

SIXTH GENERAL SESSION

Friday Afternoon, April 5, 1940

Presiding Officer

Gerald B. Webb, F.A.C.P., Colorado Springs, Colo.

p.m.

2:00 Social Components in Medicine.
EDWARD L. BORTZ, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

2:20 Illness in Families as Influenced by a Combined Medical, Psychiatric and Social Approach.
HENRY B. RICHARDSON, F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

2:40 Emotion and Bodily Changes—A Survey of Recent Psychosomatic Studies.
H. FLANDERS DUNBAR (by invitation), Associate in Psychiatry, Columbia University; Editor, Psychosomatic Medicine, New York, N. Y.

3:00 The Treatment of Illness of Emotional Origin by the Internist.
EDWARD WEISS, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia, Pa.

3:20 Post Hyperthyroid Conditions.
HENRY M. THOMAS, JR., F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

3:40 Blood Cholinesterase in Rheumatic Fever.
MARK P. SCHULTZ, F.A.C.P., Surgeon, U. S. Public Health Service, Washington, D. C.

4:05 Observations Relative to Prolonged Partial Occlusion of the Small Intestine.
LAY MARTIN, F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

4:25 Tularemic Pneumonia.
G. GILL RICHARDS, F.A.C.P., Visiting Physician, Dr. W. H. Groves, Latter-Day Saints Hospital; Member, American Board of Internal Medicine; Salt Lake City, Utah.

4:40 Bronchostenosis Complicating Allergic and Infectious Asthma.
LOUIS E. PRICKMAN, F.A.C.P., Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant, Mayo Clinic, Rochester, Minn.; and
HERMAN J. MOERSCH, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn.

5:00 ADJOURNMENT.

MORNING LECTURES

The Lectures have been of increasing popularity and are being scheduled this year between 10:00 a.m. and 12:00 m., daily, from Tuesday to Friday, inclusive. An hour is assigned to each, which permits the lecturer to complete a rounded discussion of his subject. It is true they conflict with the Clinics, but they offer a very different type of presentation and undoubtedly the Lectures will appeal to many of the members.

Each of the lecturers is an authority on the subject he will present. The topics are varied; each is important and lends itself to presentation as a well-balanced review. The colored motion pictures of the Growth of the Chick Embryo is a different type of presentation of fascinating interest.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge.

Tuesday Morning, April 2, 1940

Public Auditorium

Presiding Officer

Maurice C. Pincoffs, F.A.C.P., Baltimore, Md.

a.m.

10:00 The Diagnosis of Leukemia.
LOUIS HAMMAN, F.A.C.P., Associate Professor of Clinical Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

11:00 The Differential Diagnosis of Coronary Insufficiency.
WILLIAM J. KERR, F.A.C.P., Professor of Medicine and Chairman of Department of Medicine, University of California Medical School; Member, American Board of Internal Medicine; San Francisco, Calif.

Wednesday Morning, April 3, 1940

Public Auditorium

Presiding Officer

George Morris Piersol, F.A.C.P., Philadelphia, Pa.

a.m.

10:00 Thyroid Disease.
JAMES HOWARD MEANS, F.A.C.P., Jackson Professor of Clinical Medicine, Harvard University Medical School; Chief of Medical Services, Massachusetts General Hospital, Boston, Mass.

11:00 Problems of Acute Infections.
JOHN H. MUSSER, F.A.C.P., Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.

Thursday Morning, April 4, 1940

Public Auditorium

Presiding Officer

Edward L. Bortz, F.A.C.P., Philadelphia, Pa.

a.m.

10:00 Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra).

V. P. SYDENSTRICKER, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine; Physician-in-Chief, University Hospital, Augusta, Ga.

11:00 The Growth and Development of Chick Embryos (Motion Picture).
BRADLEY M. PATTEN (by invitation), Professor of Anatomy, University of Michigan, Ann Arbor, Mich.

Friday Morning, April 5, 1940

Public Auditorium

Presiding Officer

James E. Paullin, F.A.C.P., Atlanta, Ga.

a.m.
10:00 Polycythemia.
RUSSELL L. HADEN, F.A.C.P., Chief of Medical Division, Cleveland Clinic, Cleveland, Ohio.

11:00 Hypotension.
A. B. BROWER, F.A.C.P., Cardiologist and Member of Senior Medical Service, Miami Valley Hospital; Member of Senior Medical Staff, St. Elizabeth Hospital, Dayton, Ohio.

PANEL DISCUSSIONS

The President of the College and the Cleveland Committee on Arrangements have replaced the Round Tables with Panel Discussions at this Session. Instead of having one leader, several distinguished authorities in each of the fields will conduct the discussions. They have been requested to open the discussions promptly and to terminate them sharply at the expiration of the hour.

The Panel Discussions will be held from 1:00 p.m. to 2:00 p.m. on Tuesday, Wednesday, Thursday and Friday in the Cleveland Public Auditorium.

The leaders are prepared to discuss any phase of the subject which has been assigned to them. When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. Questions may also be submitted at least twenty-four hours before the discussion to the General Chairman. A certain number of these request questions may not be answered on account of lack of time. Leaders will answer those questions which seem to be most in demand.

Members should make application for Panel tickets on the regular application form accompanying the formal program, or at the Registration Bureau at the Public Auditorium.

PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

The staffs of seven hospitals will participate and there will be in many instances especially invited distinguished visitors to give clinics. There are eleven auditoriums available with a total capacity of 2,312. They vary in seating capacity from 60 to 400 and it will therefore be advisable to make reservations, at least for the smaller places, as soon as the formal program is received.

In addition to the clinics, there will be talks on research problems of clinical interest and on recent advances in some of the fields. This is especially true of the one morning session at the Babies and Childrens Hospital.

Details of the clinics and demonstrations will be given in full in the formal program.

PANEL DISCUSSIONS

Public Auditorium

Room	Hall "A" South Wing	Hall "B" South Wing	Clubroom "B" North Wing	Clubroom "A" North Wing
Capacity	325	325	500	225
Tuesday April 2 1:00 to 2:00 p.m.	I Edema and Nephritis Joseph M. Hayman, Jr. Louis Leiter Robert F. Loeb John P. Peters	II Drug Therapy in Heart Disease M. H. Nathanson Fred M. Smith William D. Stroud	III Vitamin B in Internal Medicine Thomas T. Mackie Julian M. Ruffin Tom D. Spies	IV Lymphomatoid Diseases Raphael Isaacs Henry Jackson, Jr. Franklin R. Miller
Wednesday April 3 1:00 to 2:00 p.m.	V Newer Drugs in Therapy M. A. Blankenhorn R. F. Parker Torald Sollmann	VI Problems in Electrocardiography Arlie R. Barnes Arthur M. Master Harold E. B. Pardee Frank N. Wilson Charles C. Wolferth	VII Allergy in Internal Medicine Robert A. Cooke Richard A. Kern Simon S. Leopold Francis M. Rackemann	VIII Industrial Diseases Daniel M. Brumfiel Leroy U. Gardner Carey P. McCord
Thursday April 4 1:00 to 2:00 p.m.	IX Gastro-Enterology Sara M. Jordan T. Grier Miller	X Hemorrhagic Diseases Charles A. Doan Harry P. Smith F. H. Taylor	XI Diabetes H. Rawle Geyelin Howard F. Root	XII Endocrinology of Puberty and Climacterium Joseph C. Aub J. S. L. Brown E. Perry McCullagh
Friday April 5 1:00 to 2:00 p.m.	XIII Problems in Tuberculosis Samuel Freedlander R. C. McKay James Alex. Miller Gerald B. Webb	XIV Physiological Aspects of Cardiac Disease Soma Weiss Carl J. Wiggers	XV Shock Treatment of Psychoses Solomon Katzenelbogen William C. Menninger S. Bernard Wortis	XVI Anemia John M. Askey Stacy R. Mettier Cyrus C. Sturgis

Special taxicab rates have been arranged between hotels and hospitals.

It will be necessary to limit admission by ticket only, otherwise there is danger that those who might wish to attend will be disappointed. Overcrowding will not be permitted. Registration blanks for the clinics and demonstrations will be distributed to all members with the formal program. These registration blanks should be filled out and returned to the Executive Secretary of the College at Philadelphia. He will select the appropriate tickets and hold them for members at the Registration Bureau in Cleveland. Reservations by mail cannot be made after March 22, but they may be made in person at the Registration Bureau not later than the evening preceding the clinic desired. Guests are urged to register for the clinics immediately after arrival in Cleveland.

CLEVELAND

WHERE WE MEET

CLEVELAND, originally a trading post at the mouth of the Cuyahoga River, has developed as the industrial center of the historic "Western Reserve." This tract of land was part of the original Connecticut charter granted in 1662 by Charles II for the whole area between the forty-first and forty-second parallels extending westward to the Pacific Ocean. In 1786 Connecticut released to the United States title to all except one area which she reserved for herself and called the Connecticut Western Reserve. This extended for 120 miles west from the Pennsylvania border, or approximately to the present city of Sandusky and just south of Akron and Youngstown.

Cleveland was developed as a planned real estate venture at the time of the great western trek into the Ohio country after the Revolution. The Public Square was laid out in 1796 by Moses Cleveland, Yale graduate and attorney. A group of hardy New England Yankees formed the Connecticut Land Company and raised a sum of $1,200,000. They were a group of substantial citizens whose names have been handed down to succeeding generations and whose descendants are still among the first families of Cleveland. Among them was Samuel Mather, Jr. who was the direct forebear of the Samuel Mather who built the present $2,500,000 medical school.

Cleveland grew rapidly because it was the natural meeting place for iron ore, coal and limestone. The Great Lakes iron ore deposits are the largest and richest in the world, some (hematite) containing 70 per cent of iron. Iron and steel have been Cleveland's leading industries since 1828 when the first smelter was established. At present her capacity is over 3,000,000 tons of pig iron annually. The first cargo of iron ore from Lake Superior entered Cleveland's harbor in 1852. In 1939 The Lake Carriers Association registered 303 ore boats, two-thirds of them over 10,000 tons. Ore by boat and coal by train meet at Cleveland blast furnaces. Huge unloaders take the ore from the ships almost a carload at a time, over 10,000 tons an hour. Today a greater annual tonnage comes from the Great Lakes to Cleveland than that of Liverpool and more than all of the French ports combined. There are fourteen miles of lakefront protected by a breakwater about six miles long; and extensive docks along the Cuyahoga River banks. The steel industry's leading technical society, The American Society for Metals, with 10,000 members, has its headquarters in Cleveland and will hold its annual "Metal Congress" in Cleveland in 1940 with an anticipated attendance of 30,000.

Cleveland industry has become most diversified, having at present 3,000 industrial plants with an aggregate annual payroll in excess of $200,000,000 and products with an annual value of $1,000,000,000. Cleveland leads in

WESTERN RESERVE UNIVERSITY MEDICAL GROUP.

From front to rear, Nurses' Home, Lakeside Hospital (with Hanna House and Institute of Pathology to right), Maternity, and Babies and Childrens Hospitals and Medical School.

In right foreground, Allen Memorial Medical Library which includes headquarters of the Academy of Medicine.

the production of all manner of iron and steel products, hardware, paint, malleable castings, electrical machinery and lamps, sewing machines, tractors and auto parts, multigraphs, telescopes, and readymade clothing. The National Electric Lamp Division of the General Electric Company has a 75-acre plant located in East Cleveland and has an elaborate research laboratory in all forms of illumination, some of real significance to medicine. There is hardly a city on the earth where Cleveland-made goods will not be found or a country whose goods are not imported to Cleveland. At least two-thirds of the nation's industries are represented in the city.

Cleveland also is the headquarters of the Fourth Federal Reserve District and as such is the financial center of this American Ruhr, the midwest manufacturing district including Pittsburgh, Youngstown, Toledo and Detroit, as busy and rich a territory as there is on the face of the earth. This Federal Reserve District is exceeded only by New York and Chicago in the United States in the volume of business.

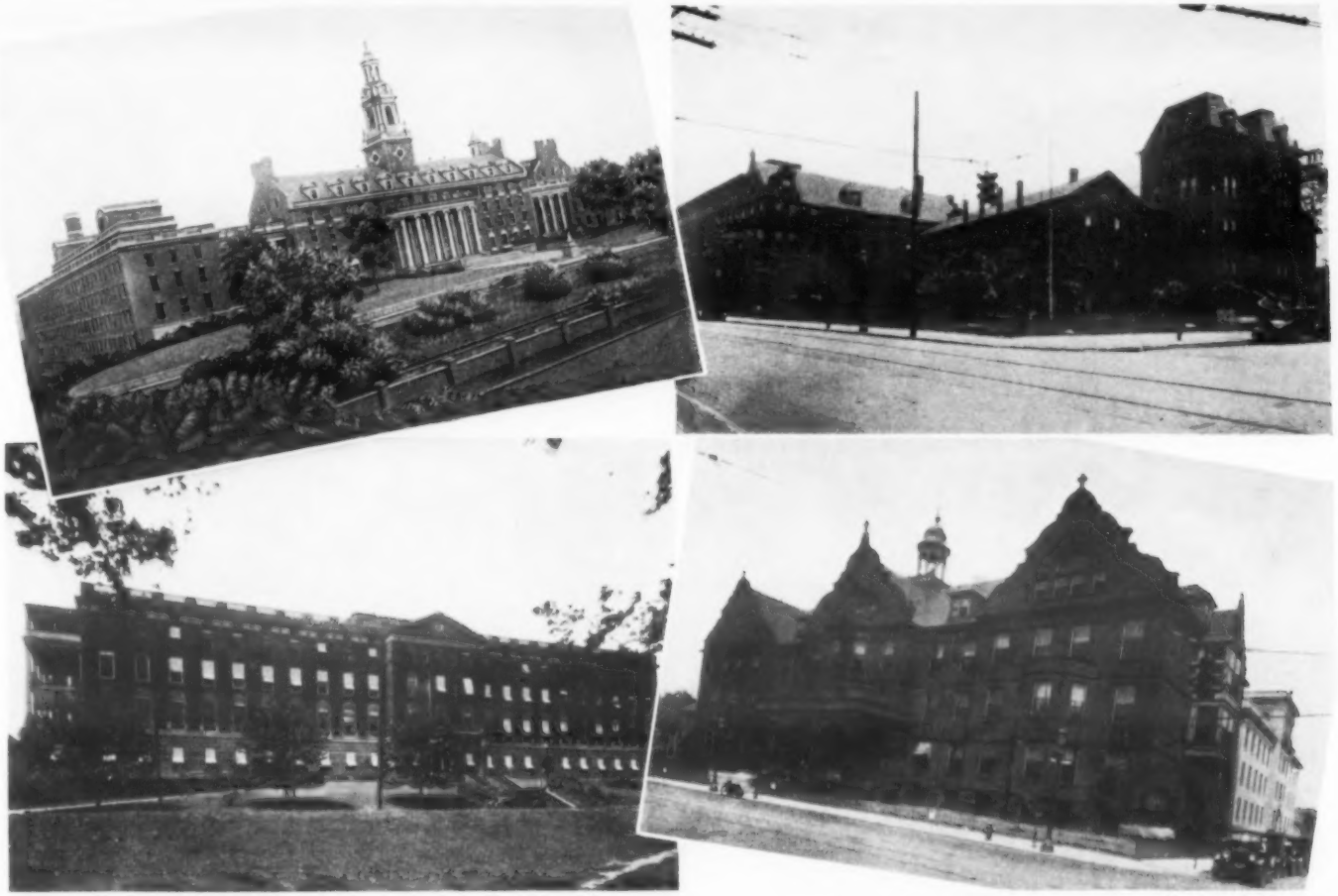
Cleveland is a natural transportation center. It is easy to reach by rail, water, air or motor. Trunk railroad lines, motor coach and airlines enter the city from all major travel centers. The New Union Passenger Terminal on the Public Square is one of the world's finest. This great building and its companion group have been called a "City Within a City." It is continuous with the Cleveland Hotel and five minutes walk from the Convention Hall. From this, Cleveland's famous Mall extends to the lake front, a $40,000,000 development covering 17 acres for a group of public buildings.

Cleveland's 1,040 acre airport is the largest municipally owned aviation field in the country and the usual site of the National Air Races. The Eastern Division headquarters of the transcontinental day and night mail route is located on the main field. Passenger and express service is available to every point in the country. The second field is occupied by the Ohio National Guard flying unit. The average ship movement is 3,500 per month. The port has twelve hangars. Service is available for all types of ships and motors. A visit to the Airport at night is most interesting. Planes may be seen landing and taking off by the light of a 500,000,000 candle power flood light.

The Metropolitan Park System of Greater Cleveland combines into one continuous outer encircling parkway the more important valleys and glens in Cuyahoga County and parts of the neighboring counties. Nine park reservations are included in the project which consists of approximately 90 miles of parkway and 15,000 acres of grounds. Two golf courses in Rocky River Valley are included in the system.

Education

Western Reserve University was established in 1826 at Hudson twenty miles to the south; and in 1882 moved to Cleveland leaving the academy at Hudson. Department after department was added until now Western



Upper Left: St. Luke's Hospital.
Lower Left: Mt. Sinai Hospital.

Upper Right: Charity Hospital.
Lower Right: St. Alexis Hospital.

Reserve University has 16 colleges and 15,000 students including downtown Cleveland College. The Medical School referred to above is one of the newest and best college medical buildings in the world and is placed in the center of a complete hospital group representing an investment of $13,000,000. Western Reserve has the only medical school in Northern Ohio, having absorbed two or more older medical schools during its growth. The famous University Circle at East 107th Street and Euclid Avenue, 3½ miles

Cleveland City Hospital Group.

east of the Public Square, includes in addition to the above the Art Museum, Severance Hall, the Medical Library, the Historical Museum and the Case School of Applied Science. In addition to Western Reserve University and Case School, Cleveland has John Carroll University, Fenn College, 300 public and parochial schools and a group of special institutes for vocational training. The Art Museum is an architectural gem in a colorful setting viewed from Euclid Avenue across the lagoon. Over 300,000 people visit the Museum annually. The city's cultural maturity is attested further by the community interest in the drama. The Play House at East 86th Street provides an outlet for local talent.

The Cleveland Orchestra has done much to carry the story of Cleveland's educational and cultural progress to the rest of the world. This famous musical organization has given concerts in more than half the states in the Union and in Cuba and Canada. Severance Hall at University Circle is the new $2,500,000 home of the Orchestra.

Unique among medical facilities in American cities is the Allen Memorial Medical Library building at the corner of Adelbert Road and Euclid Avenue. This monumental structure was made possible by a gift from Mrs. Francis

Fleury Prentiss in honor of one of the founders of the library, Dr. Dudley P. Allen, and is the official home of the practicing physicians of Cleveland. Besides the magnificent library, reading rooms and club rooms, the building houses the offices and headquarters of the Academy of Medicine (the county medical society) with auditorium facilities for groups of varying sizes. The Library, with 56,000 volumes, is one of the outstanding institutions of its kind in the country. The Academy of Medicine is a pioneer in the development of health education and community health planning in Cleveland. Its membership of nearly 1700 carries on the work in scientific sections, in numerous committees, by appointees on various welfare boards throughout the city, and by the publication of a monthly bulletin which reaches interested individuals and groups in addition to the membership. The executive office, under the direction of a full-time executive secretary, correlates all activities, and in addition furnishes a twenty-four hour call and information service for the public and the patients of Academy members.

The Cleveland Public Library, a $5,000,000 building on the Mall, is an outstanding educational feature of this city. Nine and one-half million books are borrowed from the library annually, one million educational volumes are circulated each year through its county library department. Eight million visitors enter the library each year for reading and reference.

Commensurate with the industrial, artistic and educational development, Cleveland has advanced in public health and welfare service attaining first rank in the 1939 competition for the safest and healthiest large city in the country, granted by the Chamber of Commerce of the United States in cooperation with the American Public Health Association. Cleveland's health and welfare activities are grouped under a director, at present Mr. Fred Ramsey, who is a member of the Mayor's cabinet. Health activities are delegated to the Division of Health which is under the direction of a Commissioner of Health, Dr. Harold J. Knapp. The Health Department for many years has maintained the closest coöperative relations with the organized medical profession, the Commissioner of Health meeting regularly with the Council of the Academy of Medicine and its public health and health education committees.

In Cuyahoga County there are 5,532 hospital beds exclusive of sanatoria. Greater Cleveland has a population of 1,280,000 giving an approximate ratio of hospital beds to population of 5 per 1,000. All cases of tuberculosis from Cleveland and Cuyahoga County are hospitalized by the Bureau of Tuberculosis of the Division of Health; they number at present 1,009 cases. Two hundred beds are maintained at the Contagious Division of City Hospital for quarantinable diseases.

Warrensville Farm for charitable and corrective purposes is a striking example of the spirit of Cleveland citizens. This great experiment, which has brought many students of social welfare to Cleveland, occupies 2,000 acres of high ground some seven miles from the city. Here tuberculous patients are cared for in the beautiful and well equipped Sunny Acres Sani-

torium; aged couples are enabled to spend their last years together in a cottage expressly for that purpose; and inmates of the House of Correction are taught useful occupations—in the shops in winter and in the farm fields in summer.

Unofficial health promotion agencies in Cleveland are grouped in the Cleveland Health Council as an agency under the Community Fund. This Council was organized in 1925 by the Professor of Hygiene and Preventive Medicine of Western Reserve Medical School. The Council is now composed of forty-four members. It serves to coördinate all health promotion agencies in the community including the Academy of Medicine, the Cleveland Dental Society, and eleven agencies supported by the Community Fund. The secretary of the Health Council, Mr. Howard W. Green, is an expert in census statistics and demography and carries out researches in relation to the incidence of disease and its correlation with economic factors by census tracts in the community. The findings have medical value and have led to various health education programs for parents such as those in connection with immunizations of school children.

Likewise, Cleveland has pioneered in socio-economic measures in the medical field, especially in group hospitalization and a dispensary admissions plan widely adopted and copied in the United States. The Academy of Medicine is sincerely trying to develop sound measures to adjust the form and cost of medical service to changing social needs. This policy from within the profession is regarded as the best prevention against meddlesome interference from without, especially by politically minded governmental agencies.

The Community Fund, used today by every city of consequence in the United States, originated in Cleveland. Through this centralization of social welfare financing, the amount of money realized for these important activities has been greatly increased. Citizens pledged $3,250,000 for Cleveland's 1940 welfare and relief needs. There were 490,000 donors. Before the Fund was established, 5,000 givers bore the annual burden. The Community Fund assists 100 local agencies in their welfare and relief work.

Hospitals

The medical center is at Euclid Avenue and East 110th Street. The University Hospitals of Cleveland is a non-profit corporation organized in 1925 which provides a consolidated management for four established hospitals —Lakeside Hospital, Maternity Hospital, Babies and Childrens Hospital, and Rainbow Hospital for Crippled and Convalescent Children. With the exception of Rainbow Hospital, which is located in South Euclid Village, the group is situated on the campus of Western Reserve University, with which the hospitals maintain a teaching affiliation. Here also are located the School of Medicine, the Allen Memorial Medical Library, the School of Dentistry and the Institute of Pathology where Dr. Harry Goldblatt did

GLIMPSES OF INDUSTRIAL CLEVELAND.

Upper Left: Norwegian Freighter Ties Cleveland to World Trade.
Upper Right: Lake Carrier and Loading Cranes.
Bottom: Terminal Tower Group from Public Square.

and is doing his work on hypertension and won the John Phillips prize of the College for 1938.

At Maternity Hospital, facilities are provided for the care of 75 private and 51 community service patients in the obstetrical division, and 34 patients on the gynecological service. Babies Dispensary and Hospital represent the pediatric department of the Medical School and have 75 beds. For the special benefits of its little patients, Rainbow Hospital, on Green Road, South Euclid, is built on the cottage, or one floor plan. Convalescent care is given to children crippled by infantile paralysis, bone tuberculosis, rheumatic heart disease and various nutritional deficiencies.

Cleveland Clinic Hospital.

The City Hospital, 3395 Scranton Road, sixth largest general hospital in the United States, is a municipal institution owned and operated by the City of Cleveland. It was founded in 1837 and first occupied its Scranton Road site in 1855. The present hospital group, constructed largely since 1922, covers twenty-seven acres and includes sixteen buildings with facilities for the care of 1,650 patients. The General Building (722 beds) houses the medical and surgical services, pediatrics, obstetrics, electrocardiography, and x-ray. There are, in addition, separate buildings for Contagious Diseases (200 beds), Tuberculosis (350 beds), Psychopathic Diseases (307 beds), Pathology, and the Out-Patient Department.

Top: Cleveland Museum of Art.

Center: Severance Hall (Home of Cleveland's Symphony Orchestra).

Foot: Cleveland's Public Auditorium. A unit in Cleveland's Lake Front development, it is one of a group of structures including The Court House, The City Hall, The Board of Education Headquarters, and the Municipal Stadium.

City Hospital is affiliated with Western Reserve University and is a teaching unit of the Medical School. Since 1913 the University has assumed responsibility for the professional care of patients. Visiting staff members are nominated by the faculty of the School of Medicine. In this way it has been possible to assure patients scientific treatment and to carry on medical teaching undisturbed by the political contingencies of changing city administrations. The present professional staff comprises 106 attending physicians, 95 house physicians, and 615 nurses.

In addition to University and City hospitals, medical students receive clinical instruction at Charity Hospital which was a pioneer institution dating from the Civil War period and remains as the only downtown hospital in Cleveland. It has a capacity of 300 beds and is located on East 22nd Street four blocks south of Euclid Avenue. It has very important out-patient and emergency departments.

St. Luke's Hospital is a general hospital affiliated with the Methodist Episcopal Church and has a capacity of 391 beds to be expanded ultimately to 500 beds. It is beautifully located at the entrance to Shaker Heights, residential suburb of the city of Cleveland. The building was constructed in 1927 and occupies a spacious tract of sixteen and a half acres on Shaker Boulevard at East 115th Street on the Rapid Transit Railroad. The institution, representing a value of approximately $8,000,000, is one of the largest privately endowed institutions in the country. It was made possible by the gift of Mrs. Frances F. Prentiss as a memorial building in honor of Dr. Dudley P. Allen. The hospital provides complete professional service under the three main divisions of medicine, surgery and obstetrics, with a large and well developed department of pathology.

Mount Sinai Hospital, 1800 East 105th Street, is a non-sectarian hospital founded in 1916. The present capacity of the hospital is 270 beds and comprises complete facilities for general medical and surgical services and their sub-specialties. The hospital was enlarged in 1926 by the addition of a separate out-patient department building, a nurses' home, and laboratory for pathology. The professional staff comprises 120 attending physicians and 18 house physicians. Served annually are 7,500 in-patients, 3,000 emergency patients, and 10,000 clinic patients. The hospital maintains a nurses' training school.

The Cleveland Clinic is located at Euclid Avenue and East 93rd Street. The Cleveland Clinic Foundation was organized by Dr. Frank E. Bunts, Dr. George Crile, Dr. William E. Lower and Dr. John Phillips in February, 1921, under a charter from the State of Ohio. The Cleveland Clinic Building was opened on February 26, 1921. As the activities of the Clinic expanded and the interests of the Foundation broadened, other buildings were added, the Cleveland Clinic Hospital with 225 beds in 1924, the Power Plant and Laundry in 1926, the Research Building in 1928, the new Clinic Building in 1931. The buildings house Museums of Pathology, of Intelli-

gence, Power and Personality of Man and Animals, and of Comparative Anatomy and Physiology.

St. Alexis Hospital is located in the steel mill district on the corner of Broadway and McBride Street. It is one of the city's older hospitals, dating from 1884 and has a capacity of 220 beds. It renders invaluable service to the employees of the American Steel and Wire Company, the Republic, Ohio and other Steel Companies. All general hospital services are provided except obstetrics. The staff consists of 38 visitants and 16 interns and residents.

The Cleveland Museum of Health and Hygiene, the first of its kind to be incorporated in the United States, has 521 physician members and a suitable building which should be ready for opening in 1940.

The following hospitals with locations and bed capacities are indicated for the convenience of the members of the College of Physicians. No formal demonstrations will be given, but any member desiring to visit the institutions will be welcomed.

Huron Road Hospital, 13921 Terrace Road, East Cleveland	256 beds
U. S. Marine Hospital under the U. S. Public Health Service, East 124th Street and Fairhill Road	303 beds
Glenville Hospital, 701 Parkwood Drive, North East	110 beds
Cleveland State Hospital for the Insane, Turney Road, South Side (100 acre tract of land)	2300 beds

A group of West Side hospitals with their respective capacities follows:

St. John's Hospital, 7911 Detroit	217 beds
Fairview Park Hospital, 3305 Franklin Boulevard	200 beds
Lakewood City Hospital, 14519 Detroit	176 beds
Evangelical Deaconess Hospital, 4233 Pearl Road	144 beds
Lutheran Hospital, 2609 Franklin Avenue	137 beds
Grace Hospital, 2307 West 14th Street	80 beds

The Convention Hall

The general sessions of the College of Physicians will be held in the Public Auditorium. This is one of the first structures of its kind, built at a cost of $15,000,000. Its range of service is practically unlimited. Sixteen events can be held simultaneously and without interference. The Main Auditorium seats 12,500 persons and can be readily adapted for the sessions of a huge convention. The beautiful Music Hall seats 3,000 and is well adapted to the needs of the College. The Ball Room and Little Theatre have seating capacities of 1,500 and 700 respectively; and ten other halls range in seating capacity from 90 to 500. A common stage makes it possible for the Main Auditorium and the Music Hall to seat 16,000 persons for a single event. The building is of fireproof construction and designed in Italian Renaissance architecture. The color and the diffused lighting in the main auditorium lend a warmth and softness unusual in buildings of such immense proportions. The Auditorium's acoustics have been declared perfect. The $100,000 pipe organ is one of the finest in America. Among other features

of the building are spacious lobbies and corridors, wide ramps and stairways, committee rooms, lockers, telephone booths, women's and men's retiring rooms, emergency hospital, checkroom and telegraph stations. The Hall is ideally located in the heart of the downtown district within easy walking distance of all principal hotels and shops.

The best testimonial as to the adequacy of Cleveland's convention facilities is the frequency with which the country's largest conventions and trade expositions return to this city. With half the population of the United States and Canada living within an overnight's ride, maximum attendance is a regular report at Cleveland conventions. All air and water schedules are synchronized with railroad schedules to and from all important centers so that your journey always requires the minimum of time and effort.

Cleveland's hotel accommodations for its many convention visitors are splendid. Six hotels alone have 4500 rooms—each with private bath. Designed for conventions, modern and well equipped, these hotels assist materially in making Cleveland conventions successful. Numerous assembly, banquet and conference rooms are always available. An important feature in the larger hotels is the location of the meeting rooms. None of these is located higher than the mezzanine floor, relieving the convention visitor of the annoyance of congestion at elevators.

Cleveland is expecting a record attendance at the 1940 Session of the College of Physicians. Western Reserve Medical School, the hospitals and the officers of the college are planning a program that will be in keeping with record attendance and the traditions of Cleveland medicine.

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